HOGAN & HARTSON

L.L.P.

DAVID M. FOX
PARTNER
(202) 637-5678
DMFOX@HHLAW.COM

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COLUMBIA SQUARE
555 THIRTEENTH STREET, NW
WASHINGTON, DC 20004-1109
TEL (202) 637-5600
FAX (202) 637-5910
WWW.HHLAW.COM

VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: *Docket No. 01P-0560 (CP/1)*

SUPPLEMENTAL FILING

The undersigned submits the following supplemental information in support of our citizen petition filed on December 11, 2001. The petition requests, among other things, that the Food and Drug Administration (FDA) convene an advisory committee meeting to review the pending new drug applications (NDAs) for buprenorphine for use in treating opiate addiction.

The attached information includes recent reports of serious adverse events associated with buprenorphine, particularly in countries where the drug is marketed as an addiction therapy. In France alone more than 100 deaths have been associated with buprenorphine use and abuse (*see infra*). Many of these reports may be related to an apparent synergistic effect between buprenorphine and benzodiazepines. As the Drug Enforcement Administration (DEA) recently stated:

> Many addicts and narcotic drug abusers in the U.S. and elsewhere report concurrent use/abuse of benzodiazepines. Once high dose buprenorphine is approved and generally available to these populations in the U.S., *serious overdose incidents are likely to occur.*1/

1/ Tab 1, DEA Review Document at 9 (Feb. 2002) (emphasis added).

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These and other safety issues amplify the need for FDA to obtain advisory committee review and public input before reaching a final decision on the NDAs. *See* 21 USC 393(b)(4).

Second, we have included a brief analysis of the October 2000 amendments to the Controlled Substances Act (CSA), to address concerns that FDA's authority to ensure the safe and effective use of buprenorphine has somehow been constrained. As shown, the amendments do not prevent FDA from developing a comprehensive risk management package for buprenorphine, should the agency find that the legal standard for approval can be met.

I. Recent Reports of Injury and Abuse

Since the submission of our petition, we have continued to collect information on experiences abroad involving the use of buprenorphine to treat opiate addiction. Although the drug holds great hope, it also appears to present serious risks both to the immediate user and to the community. For example:

- In France, at least 117 deaths have been associated with buprenorphine.
- In India, buprenorphine has emerged as an inexpensive street drug alternative to heroin.
- In Norway, private physicians are no longer permitted to prescribe buprenorphine for heroin addiction treatment because patients were obtaining multiple prescriptions and re-selling the drug.
- In Finland, Scotland, England, Spain, Australia, and Bangladesh, buprenorphine tablets are considered to be a recognized street drug and in France buprenorphine is known as "poor man's heroin."2/

2/ *See* Tab 2, P. Kintz, "Deaths involving buprenorphine: A compendium of French cases," *Forensic Science Int'l* 121 (2001) 65, 68 (noting that the number of fatalities is believed to e greatly underestimated); Tab 3, R.A. Singh *et. al.*, Cases of buprenorphine abuse in India, *86 Acta Psychiatr. Scand.* 46 (1992); Tab 4, L. Kumar, "Chemists selling illegal drugs to be booked," *The Times of India* (Aug. 16,

As with other drugs of abuse, these risks must be factored into the overall benefit-to-risk profile of the drug. Here, the "trade-offs" with buprenorphine are so stark that a decision to approve the drug should be made only with the benefit of advisory committee review and public input. 21 USC 393(b)(4).3/

II. The October 2000 Amendments to the CSA

In October 2000, Congress amended the CSA to relieve physicians from having to register with DEA to dispense narcotic drugs for use in maintenance or detoxification treatment. *See* The Drug Addiction Treatment Act of 2000 (the "DATA"), P.L. 106-310 (2000), amending section 303(g) of the CSA. Under section 303(g) of the CSA, as amended, a physician who meets certain specified conditions may treat a narcotic addict with a Schedule III, IV, or IV drug without having to register with DEA.

We understand there may be a concern that as a result of the DATA, the agency is prevented from applying its usual strategies for managing risks associated with drugs that pose serious and unique safety issues. In fact, the DATA does not alter FDA's legal obligation to ensure the safety and effectiveness of buprenorphine or any other drug intended to treat narcotic addiction.

2000) (reporting death from buprenorphine overdose and increase in buprenorphine addiction); Tab 5, "Buprenorphine prescription withdrawn in Norway," *Drugscope* (Sept. 21, 2001); Tab 6, World Health Organization, "Pharmaceuticals: Restrictions in Use and Availability" at 5 (Mar. 2001); Tab 7, M. Agar, *et al.*, Buprenorphine: "Field Trials" of a New Drug, *Qualitative Health Research* 11 (Jan. 2001) 69, 72, 79; Tab 8, *Report of the Int'l Narcotics Control Board for 2001*, at 33 (noting diversion and abuse in Africa, Asia and Europe).

3/ *See* FDA Task Force on Risk Management, *Managing the Risks from Medical Product Use: Creating a Risk Management Framework* (May 1999) ("As the literature points out, accurately determining the acceptability of any risk requires that the stakeholders be engaged in the process. Although there has been increasing activity in this area, FDA needs to consider expanding its efforts to involve stakeholders in the risk management process.").

The DATA essentially imposes three conditions on licensed physicians seeking a waiver of the special registration requirements under section 303(g). Under the DATA, a physician must (1) "notify" the Secretary of the Department of Health and Human Services of the intent to treat patients, (2) "qualify" by meeting certain standards, such as classroom training or adequate clinical experience, and (3) limit his or her maintenance treatment practice to 30 patients. *See* 21 USC 823(g)(2)(B) and (G). With the possible exception of physician education programs, none of these conditions interferes with FDA's general approach to managing the risks associated with a specific drug product.4/ Nor is there any evidence that Congress intended, expressly or by implication, to limit FDA's authority to ensure the safety of approved drug products. The DATA is directed at the physician; FDA, in contrast, considers the totality of the circumstances surrounding the distribution and use of the drug. 5/

The "practice of medicine" provision in section 303(g)(2)(H) of the CSA, as amended, also does not constrain FDA. Section 303(g)(2)(H)(i) authorizes the Secretary to develop practice guidelines or regulations to address the use of "credentialing bodies" to oversee narcotic treatment and to address additional exemptions the Secretary may establish regarding physician qualifications. The statute then states that "[n]othing in such regulations or practice guidelines may authorize any Federal official or employee to exercise supervision or control over the practice of medicine or the manner in which medical services are provided." *Id.* Again, this caveat is not directed at the FDA drug approval process; it is directed solely at the standards for determining whether a physician is "qualified" for purposes of the waiver provision created by the DATA.

In any case, FDA has long asserted that the types of restrictions it seeks, as necessary to ensure safety and effectiveness, do not "impermissibly interfere with the practice of medicine and pharmacy."6/ According to the agency, this is self-evident: without the restrictions, the drug product could not be approved

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4/ *See, e.g.*, Tab 9, "Risk Management Plans for Recently Approved Drugs," Briefing Book for Advisory Committee Presentation on Xyrem® (May 2001).

5/ *See* n. 3, *supra*, *Managing the Risks from Medical Product Use,* Part 1.

6/ 57 Fed. Reg. 58943, 58951 (Dec. 11, 1992).

and would not be available to practitioners to prescribe or dispense. *Id.* To the extent section 303(g)(2)(H) prohibits interference with the practice of medicine, it does not limit FDA's authority any further than the bounds of the FDCA. Thus, the types of strategies FDA generally employs for new drug products are fully available for buprenorphine. If they are not, then it is even more *unlikely* that FDA will be able to conclude that buprenorphine is safe and effective.

Finally, nothing in the DATA prevents FDA from obtaining voluntary commitments from a sponsor to limit or restrict distribution of a product, or to implement other measures to address a demonstrated safety issue. 7/

III. Conclusion

Earlier this year, the agency presented testimony on OxyContin® and acknowledged that FDA did not recognize and address in advance the risks associated with the drug.8/ FDA ought not repeat the same mistake. As one researcher has warned, "buprenorphine – like methadone before it – is no 'magic

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7/ FDA has worked with sponsors to develop: mandatory blood or urine testing as a condition for receiving a drug; mechanisms to ensure that a drug is not used in patients with certain pre-existing conditions or concurrently taking other drugs; centralized pharmacy requirements and various forms of pharmacy and patient registries; and packaging, tracer, and prescribing techniques to minimize the potential for misuse (*see, e.g.,* approvals or approvable actions for Accutane®, Clozaril®, Ticlid®, Trovan ®, Actiq®, Thalomid®, Ziagen®, Mifeprex®, and Xyrem®). None of these measures is in any way blocked by the DATA.

8/ Tab 10, FDA Testimony before the U.S. Senate Comm. on Health, Education, Labor and Pensions (Feb. 12, 2002) ("At the time of approval, the abuse potential for OxyContin *was considered by FDA* to be no greater than for other Schedule II opioid analgesics . . . . [T]he widespread abuse and misuse of OxyContin that has been reported over the past few years *was not predicted.* In fact, at the time of its approval, *FDA believed that the controlled-release characteristics of the OxyContin formulation would result in less abuse potential* . . . ." (emphasis added)).

bullet.' Unrealistic expectations for success that neglect the realities and needs of the streets only yield surprises that could have been anticipated."9/

The advisory committee process, with opportunity for public input, will only help FDA to anticipate the risks associated with buprenorphine and test the assumptions that are critical to determining whether high dose buprenorphine tablets should be approved for use in the United States.

IV. Environmental Impact

The actions requested in the petition are not within the categories for which an environmental assessment is required pursuant to 21 CFR 25.22.

V. Economic Impact

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

VI. Economic Impact

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition

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9/ Tab 7, *supra*, at 80-81.

relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

David M. Fox
HOGAN & HARTSON L.L.P.
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004-1109
(202) 637-5678

Enclosures

cc(w/encls.): Steven K. Galson, M.D.
Cynthia G. McCormick, M.D.
Janet Woodcock, M.D.

Buprenorphine
DEA Review Document
Scheduling Under the CSA
February 2002

Introduction:

Buprenorphine is a derivative of thebaine, a major constituent of opium. As such, it was controlled in Schedule II of the Controlled Substances Act (CSA) in 1970 and remained in Schedule II during its research and development for marketing. In 1981, buprenorphine hydrochloride (Buprenex®) was approved for use in the United States as an analgesic. In 1982, the Assistant Secretary of Health, Edward N. Brandt, Jr., recommended that buprenorphine be placed in Schedule V of the CSA. This recommendation was based on findings that buprenorphine had an approved medical use in the United States and that its abuse potential was low and consistent with Schedule V placement. The Drug Enforcement Administration (DEA) published a proposal to place buprenorphine in Schedule V in 1982 but this rulemaking was not finalized until April 1, 1985 (50 FR 8104) due to a lengthy formal hearing that was initiated by Reckitt & Colman (now Reckitt Benckiser), the patent holder and manufacturer for buprenorphine worldwide. The company's objection to the proposal was based on their contention that buprenorphine did not have sufficient potential for abuse to warrant Schedule V placement in the CSA and that buprenorphine should not be classified as a narcotic as defined by the CSA. Data was provided from several countries including West Germany, Australia and New Zealand (where buprenorphine had been available for a limited period of time) showing buprenorphine abuse, diversion and trafficking. In addition, buprenorphine was established as an opiate and morphine-like substance derived from thebaine, thereby meeting the definition of narcotic under the Act. The Schedule V control of buprenorphine and its designation as a narcotic under the CSA was upheld by the Administrative Law Judge, Francis Young.

Buprenex® is an injectable formulation (0.3 mg/ml) intended for intravenous or intramuscular administration for the treatment of moderate to severe pain (analgesic potency is far greater than morphine sulfate: generally reported as about 20 to 30 times more potent than morphine in humans). Until recent clinical trials with sublingual (substance placed beneath or under the tongue) buprenorphine, this injectable formulation has been the sole product available in the United States. Buprenex® has had limited distribution (available primarily as an in-patient medication through hospital pharmacies) and very little prescription ( ). No significant diversion/abuse of this product have been documented in the U.S.

Two New Drug Applications (NDAs) for buprenorphine products have been submitted to the Food and Drug Administration (FDA). For the last several years, the National Institute on Drug Abuse (NIDA) has been working with Reckitt Benckiser under a Cooperative Research and Development Agreement (CRADA) to develop buprenorphine products for the treatment of opioid addiction. These NDAs are for high-

dose sublingual buprenorphine single entity tablets (Subutex®) and high-dose sublingual buprenorphine/naloxone combination tablets (Suboxone®). Both buprenorphine products (single entity and combination) are for 2 and 8 mg sublingual tablets. Compared to the approved dosage strength of Buprenex® (0.3 mg/ml with a maximum recommended dose of 0.6 mg), these new products are considerably more potent. The Subutex and Suboxone NDAs remain pending at FDA but approvable letters have been issued for both products and they are likely to receive final marketing approval in 2002.

The maintenance treatment for narcotic addiction has been subject to strict control, regulation and treatment standards for nearly three decades under the Narcotic Addict Treatment Act of 1974. In October 2001, Congress amended the CSA to allow qualified physicians, under certification by the Department of Health and Human services (DHHS), to prescribe Schedule III-V narcotic drugs (FDA approved for the indication of narcotic treatment) for narcotic addiction outside the context of clinic-based narcotic treatment programs (Pub. L. 106-310). Once approved for use, the new buprenorphine products (if not placed in Schedule II of the CSA) would be the only treatment drugs that meet the criteria of this exemption (the only other approved narcotic treatment drugs in the U.S. are LAAM and methadone and they are in Schedule II of the CSA). Buprenex®, the currently marketed buprenorphine product, is not approved for use in treating opioid addiction. This office-based treatment approach is likely to result in the availability of large amounts of buprenorphine in the United States.

A substantial amount of human experience with buprenorphine products as well as a number of controlled clinical research studies have become available since the original scheduling action for buprenorphine in 1985. On December 4, 2001, the DHHS signed and forwarded a letter to the DEA recommending that buprenorphine be rescheduled to Schedule III of the CSA based on an attached document containing their scientific and medical evaluation for buprenorphine (see attachments). After considering the DHHS scientific and medical data and rescheduling recommendation and reviewing all the relevant data regarding the eight factors determinative of control (21 U.S.C. 811 (b)(c)), the DEA Office of Diversion Control believes that the available data warrants the increased control of buprenorphine. In addition to the DHHS review document, the following is a summary of the information used to conclude that buprenorphine should be placed in Schedule III of the CSA.

Factor 1: The drug's actual or relative potential for abuse

The evaluation of the abuse potential of any substance considers a number of factors including (but not limited to) its pharmacology, profile of effects under various conditions, physical and psychological dependence liability and actual abuse data.

Pharmacological Effects:

Buprenorphine is classified as a partial agonist of the opioid receptor (maximal effects are less than those of full agonists). However, despite its partial agonist activity,

data indicates that, under most conditions, buprenorphine's physiological and psychological effects are essentially the same as morphine or hydromorphone (pure opioid agonists); producing dose-related euphoria, drug liking, pupillary constriction, respiratory depression and sedation. However, acute high doses of buprenorphine have been shown to have a blunting (plateau) effect on both physiological and psychological effects (Walsh et al., 1994,1995).

Discriminitive stimulus and self reported effects:

Drug discrimination studies are among the most rigorous laboratory procedures for assessing the substitutability of psychoactive drugs (Schuster & Johanson, 1988) and provide valuable information about the subjective effects of these drugs. Buprenorphine generally substitutes for other mu agonists in drug discrimination studies across several species including humans (for example: Leander, 1983; France et al., 1984; Young et al, 1984; France & Woods, 1985; Hoffmeister, 1988; Picker & Dykstra, 1989; Negus et al., 1990; Negus et al., 1991; Preston et al., 1987, 1989, 1992; Bigelow and Preston, 1992, 1994; Paronis & Holtzman, 1994; Walker et al., 1994). These studies suggest that buprenorphine shares more discriminative stimulus effects with pure mu agonists than with prototypic partial agonists. For example, Preston & Bigelow (2000) conducted a drug discrimination study in adult males with histories of opioid abuse (but not physically dependent at time of study) trained to discriminate hydromorphone from placebo (saline). Of the partial agonists tested (buprenorphine, butorphanol, pentazocine and nalbuphine) only buprenorphine produced dose-related increases in hydromorphone-appropriate responses.

The subjective effects of buprenorphine with or without naloxone have been studied in a number of different populations, across different dose ranges and routes of administration and for various periods of time. In addition, opiate or naloxone challenge in buprenorphine maintained clients varies significantly with study conditions. Despite these methodological differences, certain conclusions can be made regarding the abuse potential of buprenorphine (with or without naloxone) in different populations of users. The following represents a sampling of studies in three different populations: (1) non-drug abusers; (2) experienced opiate abusers not opiate dependent at time of study; and (3) opiate-dependent (addicts/treatment clients).

Studies conducted in non-drug abusers (for example: Blom et al., 1987; Manner et al., 1987; Saarialho-Kere et al., 1987; Gal, 1989; MacDonald et al., 1989; Timm et al., 1991; Zacny et al., 1997) indicate that buprenorphine, like morphine, produces dose related impairment of psychomotor performance, euphoria, somnolence and nausea. At equianalgesic doses, buprenorphine can produce greater effects (both qualitative and quantitative) than morphine. For example, Zacny and associates (1997) found that 0.3 mg intravenous buprenorphine produced a larger magnitude of effect on mood, psychomotor performance and pupil constriction than an equianalgesic intravenous dose of morphine (10 mg). In another study with opiate-free detoxified heroin abusers, buprenorphine (0.6 mg, intramuscularly) was identified as heroin, was liked better than

equianalgesic doses of morphine or pentazocine and caused considerable euphoria (Bedi et al., 1998). These data suggest that buprenorphine may be very reinforcing when administered to drug naïve individuals and experienced non-dependent opiate abusers.

In studies with opiate users, the most consistent finding with buprenorphine administration is a dose-related increase in drug-liking and good drug effects (for example: Jasinski et al., 1978; Jasinski et al., 1989; Preston et al., 1989; Preston et al., 1992; Weinhold et al., 1992; Pickworth et al., 1993; Preston and Bigelow, 1994; Walsh et al., 1994, 1995; Foltin and Fischman, 1994, 1995; Greenwald et al., 1999).

Jasinski et al (1978) conducted the original clinical abuse liability studies evaluating buprenorphine's abuse potential in narcotic addicts and assessed its possible utility in the treatment of narcotic addiction. Buprenorphine was shown to produce morphine-like subjective, behavioral and physiological effects and morphine-like physical dependence. Administered chronically in a single daily subcutaneous dose of 8 mg, buprenorphine produces subjective effects and euphoria equivalent to 30 mg of morphine sulfate administered subcutaneously four times daily or a 30 to 60 mg oral single daily dose of methadone. The abstinence syndrome observed after abrupt withdrawal of chronically administered buprenorphine was delayed producing peak Himmelsbach abstinence scores after about two weeks. Peak withdrawal effects were clinically significant but of lesser magnitude than pure mu agonists. Four mg of naloxone subcutaneously did not precipitate abstinence and morphine challenges of 15 and 30 mg subcutaneously produced significantly attenuated opioid agonist effects.

In a study conducted by Greenwald, Johanson and Schuster (1999), the reinforcing effects of varying intramuscular injections of hydromorphone were evaluated in opioid dependent volunteers maintained on varying doses (2, 4, and 8 mg) of sublingual buprenorphine. Mean ratings of "high" significantly increased as a function of hydromorphone dose and buprenorphine dose-dependently reduced opioid symptoms only at the hydromorphone 16 mg dose. Interestingly, volunteers who were non-abstainers (having opioid positive urines during the maintenance phase of buprenorphine treatment prior to hydromorphone challenge) had significantly greater morphine-like effects across all measures as compared to abstainers (clean urines during maintenance). In a study to determine what dose of buprenorphine would effectively block the reinforcing effects of intravenous heroin (Comer et al., 2001), both 8 and 16 mg of sublingual buprenorphine maintenance dosing failed to block the effects of 12.5 mg or 25 mg I.V. heroin. These data indicate that buprenorphine maintenance (even at relatively high maintenance doses) may not serve as a deterrent for patients who chose to continue their illicit use of heroin or other opiates.

Strain et al. (1997) conducted a study to determine the abuse liability of parenteral buprenorphine in eight volunteers maintained on daily sublingual buprenorphine (8 mg). Medication challenges were tested 16h after the daily dose of buprenorphine and consisted of double-blind IM injections of 4, 8, and 16 mg of buprenorphine or 9 and 18 mg of hydromorphone. Supplemental IM doses of buprenorphine produced dose-dependent increases in opioid agonist rating and subjective effects. Hydromorphone

challenge was not blocked (still capable of producing increased agonist effects) although there was a lack of dose-related increases in effects. This data suggest that buprenorphine-maintained patients (even at high maintenance doses) may abuse additional buprenorphine or other opiate drugs for their reinforcing effects.

Mendelson et al (1999) studied the effects of three intravenous buprenorphine and naloxone combinations on agonist effects and withdrawal signs in 12 opiate-dependent subjects. Following stabilization on a daily dose of 60 mg morphine intramuscularly, subjects were challenged with buprenorphine alone (2 mg) or in combination with naloxone in ratios of 2:1, 4:1, and 8:1 (1, 0.5, and 0.25 mg of naloxone). Buprenorphine alone did not precipitate withdrawal and produced effects similar to morphine. Dose-dependent increases in withdrawal signs and symptoms and a decrease in opioid agonist effects occurred after all naloxone combinations. At the 4:1 ratio (that which has been chosen for the marketing of the combination product), opioid agonist effects were attenuated by about 50 % and unpleasant effects were observed for about 15 to 30 minutes. These data suggest that injection of the combination buprenorphine/naloxone product may be less desirable to non-buprenorphine opiate dependent addicts. Data from New Zealand, where a naloxone-combination product has been marketed, show that the combination product is still injected and abused by street addicts although it is injected and abused less than the single entity product.

Eissenberg et al (1996) found that subjects maintained on 8 mg of sublingual buprenorphine had no significant withdrawal signs (any drug effect, bad drug effect and increases on the withdrawal adjective scale) when 0.3 mg or 1.0 mg of naloxone was administered intramuscularly (IM). Three mg of IM naloxone produced significant withdrawal signs in this population. This study suggests that high concentrations of naloxone are needed to precipitate withdrawal in some populations of buprenorphine maintained clients. As a consequence, injection of Suboxone® may not result in significant withdrawal signs and may be very attractive to some populations of narcotic abusers and addicts. In addition, this data suggest that naloxone may not be effective in reversing respiratory depression in buprenorphine overdose. Indeed, clinical studies have demonstrated that naloxone has not been effective in reversing the respiratory depression associated with buprenorphine administration (Thorn et al., 1988).

Intramuscular administration of buprenorphine alone (0.4 and 0.8 mg/70 kg) or in combination with naloxone (0.4 and 0.8 mg/70 kg) was examined in seven non-physically-dependent opioid abuser volunteers (Weinhold et al, 1992). These data show that, at some concentrations, the addition of naloxone to buprenorphine actually potentiates the morphine-like subjective effects of buprenorphine. In subjective measures of drug effects, buprenorphine alone produced dose dependent increases in "liking," "high," and agonist ratings. Administration of 0.4 mg buprenorphine in combination with 0.4 mg naloxone produced positive subjective opiate effects greater than 0.4 mg of buprenorphine alone and a greater percentage of subjects identified the naloxone-buprenorphine combination as an opiate when compared to buprenorphine treatment alone.

In summary, these papers and other buprenorphine studies indicate that buprenorphine products may be sought by a wide variety of narcotic abusers. The significant "morphine-like" effects produced by buprenorphine in most populations of narcotic abusers provide valuable information regarding buprenorphine's abuse potential. Fraser (1968), Jasinski (1973) and Holzman (1977) have all concluded that the abuse potential of narcotic analgesics are a critical function of the nature of their subjective effects. These authors have concluded that the best predictor of an opiate's abuse liability is the identification of a drug as opiate-like by narcotic abusers. The perception of buprenorphine as "heroin, morphine or hydromorphone-like" by experienced opiate abusers, as well as drug naïve individuals, suggest that buprenorphine can serve as a positive reinforcer for drug seeking behaviors in both the presence and absence of naloxone. Data have also suggested that injection of the buprenorphine and naloxone combination products can produce significant dysphoric effects in some populations of non-buprenorphine maintained narcotic-dependent addicts. However, in other populations of drug abusers, this drug combination is usually reinforcing when taken orally or by injection.

Buprenorphine's actual abuse:

While a comprehensive summary regarding buprenorphine abuse is provided in Factor 4, a brief summary of that data will be provided here.

Starting in the late 1970s, low-dose buprenorphine sublingual tablets and injectable solutions were approved for marketing in many countries (See DHHS Document Table 1). High-dose buprenorphine for narcotic treatment gained marketing approval in France in 1996 and has since been approved in several other countries. As a partial agonist, buprenorphine was originally believed to have significantly less abuse potential than pure mu agonists, like morphine. As a consequence, most countries initially marketed this drug without any significant control measures. However, reports of buprenorphine abuse occurred shortly after it became available in various countries and in some localities buprenorphine is the preferred drug of abuse. Austria, Australia, Germany, France, New Zealand, Norway and India have all increased the regulatory controls on buprenorphine as a consequence of significant diversion and abuse of this drug.

Data from the abuse literature indicate that:

- Buprenorphine has been abused by various routes of administration (sublingual, intranasal and injection) and has gained popularity as a heroin substitute as well as a primary drug of abuse.
- Large percentages of the drug abusing population in some areas of France, Ireland, Scotland, India and New Zealand have reported abusing buprenorphine often by injection and often in combination with benzodiazepines.
- Buprenorphine is abused by a wide variety of abusers: young drug naive individuals, non-addicted opiate abusers, heroin addicts and buprenorphine treatment clients.

- Many clinicians and researchers urge stricter controls for buprenorphine and/or urge caution with the use of this drug.

Information regarding the use of high-dose buprenorphine sublingual tablets (2 and 8 mg) is available from France (as yet, no data is available from other countries that have started to market the high dose sublingual tablets for addiction treatment). The French experience is particularly informative and provides valuable information about the use of high-dose sublingual tablets in a setting very similar to what is envisioned for Suboxone® and Subutex® in the U.S. The following information was

Subutex® was approved for use in France in February 1996. Any doctor can prescribe high-dose buprenorphine for up to 28 days per prescription (must use a counterfoil prescription book specifically designed for narcotic drugs and monitored by the French Medical Association) and any pharmacy can dispense Subutex® (Brunelle, 1998). This system of treatment is a considerable departure from previous policy. Prior to 1996, France provided very limited treatment with methadone in state-run clinics (on a per capita basis, France had the lowest narcotic treatment of any European country). The spread of HIV and other communicable diseases by intravenous drug users, the acceptance of various types of narcotic replacement treatment in other countries (methadone, morphine, heroin and low-dose buprenorphine) combined with data suggesting that high-dose buprenorphine was a safer treatment drug, set the stage for France's new policy.

A multidisciplinary task force (working under an agreement with the Office of the Junior Minister for Health, the General Health Administration and Schering Plough Laboratories) reported on the use of Subutex® in France (INSERM, June 1998). The objective of the task force was to produce a summary of the knowledge gained from the basic and clinical perspective and from a public health standpoint to assess the advantages, risks, and effectiveness of substitution treatment in France. Data presented in the report suggested that trafficking in heroin and heroin overdose deaths significantly declined in France since Subutex® became available (although no analysis was done to determine if other European countries may have experienced a similar reduction in heroin trafficking and deaths). However, data also showed that Subutex® use is associated with significant public health risks. The following points were made by the task force:

- As an agonist/antagonist or partial agonist, buprenorphine is purported to have less abuse liability. However, buprenorphine's physiological and psychological effects are essentially the same as morphine or hydromorphone.

- The use of benzodiazepines in combination with buprenorphine products is frequently encountered (both self-reports of addicts and studies have verified the frequency of this combination: about 20 to 44 % of addicts treated with Subutex® also administer benzodiazepines). This combination poses additional risks for both dual addiction as well as the risk of respiratory failure and death. (From February 1996 to October 1997, health officials were aware of 17 deaths associated with this combination).

- Sales of syringes have remained stable despite the large numbers of individuals in treatment with Subutex® (50,000 buprenorphine-treated patients in 1997). Addicts report that they continue to inject, often crushing, dissolving and injecting their buprenorphine tablets as well as other drugs of abuse.

- Survey data indicated that general practitioners are unable to obtain psychological services for their patients, as few psychiatrists will treat intravenous drug users (less than 1% of the psychiatrists are linked to addiction treatment or have experience in treating addiction).

- Subutex® has been diverted and abused by a significant percentage of individuals receiving buprenorphine prescriptions:

    - 12 to 31 % inject their own medication
    - 2 to 9 % get multiple prescriptions from 2 or more physicians

- Young abusers, not yet addicted to narcotics, are using buprenorphine as a "gateway" drug (the degree to which this occurs is unknown).

The most recent data regarding Subutex® use in France is provided by Thirion et al. (2002), who conducted an analysis of 11,186 buprenorphine prescriptions (written between September through December 1999) to determine how buprenorphine was being used by French practitioners. Eighty five percent of the buprenorphine prescriptions were written by general practitioners who often prescribed for only one or two patients. The mean dose was 11.5 mg per day, 12 % of the patients received prescriptions from more than two prescribers and 43 % of the maintained patients had an associated benzodiazepine prescription, often on the same prescription form. Sixty one percent of patients had regular follow-up, 21 % had occasional consultations and 18 % had deviant maintenance treatment (more than two prescribers or more than 20 mg per day of buprenorphine). The authors concluded that the easy access to maintenance treatment in France is associated with a high risk of buprenorphine abuse.

A number of studies have examined buprenorphine-related deaths. In a compilation of the case reports and analysis involving buprenorphine overdoses in France (29 non-fatal and 20 fatal occurring between February 1996 and October 1997 at the hospitals and forensic laboratories in Strasbourg, France), Tracqui and colleagues (1998) speculated that the high dosage of Subutex® tablets is likely to play a role in the occurrence of accidents in spite of the theoretical "ceiling effect" (see Factor 2.). However, almost all cases involved diverted medication and the use of other psychoactive drugs, especially benzodiazepines. Intravenous injection of the crushed tablet also appears to be a risk factor and was associated with 8 deaths and 10 non-fatal overdoses.

Kintz (2001) reported an additional 117 deaths involving buprenorphine that were observed at the Institute of Legal Medicine of Strasbourg from March 1998 – July 2000

(39 cases) and at 13 other French forensic centers from mid 1996 - March 2000 (78 cases). Eighty two percent of the cases involved males. Needle marks suggesting recent intravenous injection(s) were observed in about half of the subjects. All but one case involved concomitant intake of other psychotropic substances. Benzodiazepines were most commonly found in combination with buprenorphine (91 cases). The author concluded that intravenous injection, concomitant use of CNS depressants (especially benzodiazepines) and high-dose buprenorphine formulation were risk factors in buprenorphine-associated fatalities. He further concluded that the total number of buprenorphine-related deaths in France is probably underestimated due to: (1) the drug is difficult to analyze (low concentration and no immunoassay in France); (2) only some forensic centers responded to the question of fatalities involving buprenorphine; and (3) in numerous cases, an obvious overdose (known drug addict, presence of syringe or packages of Subutex®), no autopsy is requested by the police or a judge.

Buprenorphine overdose has been reported in other countries. In a study of 1018 drug injectors recruited in Glasgow during 1993 and 1994, 413 injectors reported using buprenorphine (41 %) and of those, 26 % reported at least one overdose (Taylor et al, 1996). Thorn et al (1988) discussed a study using buprenorphine for postoperative pain that had to be abandoned when 3 of the first 16 patients showed signs of late-onset respiratory depression lasting for 6-7 hours that did not respond to naloxone. In June of 1987, as a result of 10 cases of severe respiratory depression, the Swedish Health Board issued a warning to Swedish physicians regarding the association of respiratory depression and buprenorphine administration.

In summary, the DEA concurs with DHHS in their assessment that buprenorphine has a high potential for abuse based on the following findings:

- There is significant evidence that individuals have taken buprenorphine in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community. For example, buprenorphine overdoses and related deaths in France suggest that high-dose buprenorphine abuse by individuals likely to abuse other CNS depressants (benzodiazepines in particular) is associated with considerable risk. Many addicts and narcotic drug abusers in the U.S. and elsewhere report concurrent use/abuse of benzodiazepines. Once high dose buprenorphine is approved and generally available to these populations in the U.S., serious overdose incidents are likely to occur.

- There has been significant diversion of buprenorphine from legitimate channels in countries where buprenorphine has been more available in both sublingual tablets and injectable formulations. Increased availability of buprenorphine is likely to occur with the approval of high-dose buprenorphine for addiction treatment in office settings. The DHHS makes a compelling argument for increased controls based on U.S. experience with other narcotic drugs (i.e. butophanol) that were marketed without significant diversion until a new formulation became available having greater distribution and acceptance as a drug of abuse. According to DHHS, "dramatic increases in abuse and diversion have been observed following approval and

marketing of older drugs due to changes in dose and formulation, as well as market expansion" (see DHHS document). Among the many factors that can influence the acceptability of a drug by the drug abusing population, the availability of a drug, formulation, route of administration and dose all play significant roles (see Factor 2).

- Individuals have taken buprenorphine on their own initiative without medical advice. In many countries, buprenorphine has become a significant drug of abuse and has been associated with considerable diversion from legitimate channels as documented by law enforcement encounters, drug control authorities and published literature. The fact that the new high-dose buprenorphine products are intended for prescription by physicians who may not have extensive experience in dealing with this patient population and use by addicts who are likely to abuse/divert their medications, in the absence of enforceable minimal standards of treatment, increases the likelihood of diversion and abuse of this drug.

- Buprenorphine shares a number of properties with known drugs of abuse. It produces euphoric effects similar to hydromorphone and, in most populations, buprenorphine is recognized as morphine or heroin-like.

Factor 2. Scientific evidence of its pharmacological effect, if known

Buprenorphine is a long-acting partial *mu* opioid agonist and *kappa* opioid antagonist with very high affinity for both receptors (Cowan et al., 1977a). It is referred to as a mixed agonist/antagonist or partial agonist at opioid receptors. Unlike morphine, a pure *mu* agonist, and pentazocine, a mixed agonist-antagonist, buprenorphine binds tenaciously to opioid receptors for very long periods (24 to 72 hours) and high doses of naloxone are needed to displace buprenorphine from the receptor (for example: Knape, 1986; Fudala et al., 1990; Eissenberg et al., 1996)

In animal studies, buprenorphine produces a bell-shaped respiratory depressant curve (Rance et. al., 1985). At low to intermediate doses, buprenorphine produces about the same amount, or greater, respiratory depressant effects as equianalgesic doses of morphine. However, as the dose is increased to relatively high levels, the amount of respiratory depression produced by buprenorphine levels off. This "ceiling effect" is why buprenorphine is thought to be significantly safer in overdose relative to other narcotic treatment drugs and may result in less abuse potential than other pure mu agonists in Schedule I or II of the CSA. In clinical studies, buprenorphine produces morphine-like effects dose-dependently up to about 8 mg. Somewhere between 8 mg and 16 mg, buprenorphine effects start to be less dose-dependent with effects somewhat attenuated as compared to morphine suggesting that the purported "ceiling effect" may also be operative in human subjects (Jasinski et al, 1978; Bigelow and Preston, 1992; Strain et al., 1999).

The entire class of drugs referred to as mixed agonist-antagonists or partial agonists have had a long history of uncertainty regarding the extent to which their pharmacological activity may influence their abuse potential. They were developed in an attempt to provide novel analgesia with little or no abuse potential and fewer side effects than pure mu agonists. The premise was that a drug having mixed agonist-antagonist activity would be an effective analgesic at low to moderate doses but any further increase in dosage would not produce pleasurable effects of a morphine-like drug and would not substitute for morphine/heroin nor produce physical dependence.

Pentazocine was the first drug of this class to be marketed in the U.S. and was initially available as an uncontrolled injectable formulation. Very little prescription and abuse were initially identified. Significant abuse of pentazocine occurred soon after it became available in a tablet for oral administration and was later (1979) controlled under the CSA as a Schedule IV substance. Compared to buprenorphine, it is considerably less potent as an analgesic, has a shorter duration of action (2 – 4 hours), will not substitute for morphine in morphine-dependent individuals and is associated with significant dysphoric effects at high doses (Jasinski et al., 1970). Despite some of these less desirable effects, pentazocine became a very popular street drug and was often abused in combination with tripelennamine, referred to as "Ts and Blues" among abusers who often injected this combination to get what they reported as a heroin-like high. Control in Schedule IV of the CSA was insufficient to curb the growing abuse of this substance. As a consequence, the single entity pentazocine was removed from the market and replaced with a naloxone-combination product.

Another agonist-antagonist, butorphanol, had a similar profile of use and abuse. It was also initially marketed as an injectable medication for the treatment of pain. For years, little abuse or diversion of this product were identified. However, the introduction of a nasal spray product in 1992 marked the beginning of large increases in sale, distribution and prescription of butorphanol. It also marked the beginning of significant reports of abuse and diversion (see DHHS document). Compared to pentazocine (50 mg orally), butorphanol (4 mg orally) has about an equivalent analgesic potency (Levin et al., 1978). At equivalent doses, butorphanol produces greater aversive or dysphoric effects than morphine (Zacny et al., 1994). In monkey and humans, butorphanol substituted for other mixed agonist-antagonists (Schaefer and Holtxman, 1978; Preston et al., 1989) and was discriminated as pentazocine-like (Preston et al., 1989). Unlike buprenorphine which is recognized as morphine or hydromorphone-like in a number of paradigms (see Factor 1), physically dependent subjects trained to descriminate among naloxone, hydromorphone and saline, butorphanol was descriminated as naloxone-like (antagonist-like)(Preston et al., 1990; Preston and Bigelow, 1990).

These data indicate that buprenorphine produces effects that are generally more morphine-like than other mixed agonist-antagonists but share some "ceiling effect" properties with other agonist-antagonists. This data also shows that the availability and formulation of drugs with abuse potential play a significant role in the extent to which a drug is abused.

Other Pharmacological effects:

Buprenorphine is extensively metabolized by the liver to its major metabolites: norbuprenorphine (N-dealkylbuprenorphine) and glucuronides of buprenorphine. Norbuprenorphine has high affinity for mu-, delta-, and kappa-opioid receptors comparable to buprenorphine, has a very long half-life, is a full mu agonist with low intrinsic activity and may contribute to the unique pharmacological profile of buprenorphine (Huang et al., 2001). Buprenorphine is primarily (70%) excreted via the feces (greatest amount 4 to 6 days following buprenorphine administration) but metabolites of buprenorphine can be detected in the urine (Cone et al., 1984). As yet, there is no commercial urine test available for doctors to readily determine medication compliance or abuse. High doses of buprenorphine may cause liver toxicity by impairing mitochondrial respiration and ATP formation (Berson et al., 2001). Risk factors for liver toxicity include intravenous abuse and overdose. Buprenorphine crosses the blood-brain barrier and the placenta. Effects on the unborn fetus are not well established although a narcotic abstinence syndrome has been reported in neonates (See Factor Factor 6 DHHS Review).

The absolute bioavailability of the sublingual tablets is about 30 % (Mendelson et al., 1997). Saliva buprenorphine concentrations may have contributed to the almost twofold overestimation of the bioavaiability of buprenorphine as previously reported. The bioavailability of the sublingual tablet is about 50% that of the sublingual alcoholic solution containing equivalent amounts of buprenorphine (Nath et al., 1999: Schuh et al., 1999). As a consequence, data generated using the sublingual alcoholic solution may not reflect the effects of similar doses of sublingual tablets.

Factor 3: The state of current scientific knowledge regarding the substance

Buprenorphine is a thebaine-derived narcotic currently controlled in Schedule V of the CSA. The hydrochloride salt is a white crystalline powder having a molecular formula of $C_{29}H_{41}NO_4.HCl$ with a molecular weight of 504.11. Drug product is the hydrochloride salt known chemically as 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol hydrochloride. It has been approved for use as an injectable analgesic and the sublingual tablets for narcotic treatment have been approved in many countries and are likely to be approved for use in the U.S. The hydrochloride salt of buprenorphine is sparingly soluble in water, but soluble in methanol or ethanol. To date, no clandestine production of buprenorphine has been identified.

Buprenorphine is controlled in Schedule III of the Psychotropic Convention of 1971 as a non-narcotic but is under review for inclusion in the Single Convention for Narcotics due to continued concern about its diversion and abuse.

Factor 4: Its history and current pattern of abuse

United States:

Buprenorphine (Buprenex®) has been marketed in the U.S. since 1984 as an analgesic in an injectable formulation at a concentration of 0.3 mg/ml. This product has had limited distribution (found primarily in hospital pharmacies and clinics) and little prescription (about 38,000 prescriptions in 2000). The relatively small amounts of diverted drug and the limited number of law enforcement encounters is consistent with its limited availability in the U.S. In the last five years (1997-2001), DEA laboratories have analyzed buprenorphine exhibits involving 657 vials of the injectable formulation and 653 tablets from 16 separate cases. Many of the pills have been illicitly smuggled into the U.S. from Mexico.

Other Countries:

Early unpublished reports of buprenorphine abuse in Austria, Germany and New Zealand were made available to the U.S. during the legislative hearing that resulted in the initial scheduling of buprenorphine in the CSA (1984). Published reports of buprenorphine abuse are numerous and many countries are represented. The following is a sampling of articles and reports regarding the abuse of buprenorphine.

Buprenorphine abuse in the United Kingdom was first reported by Strang (1985). Sublingual tablets (0.2 mg) were being crushed, solubilized and injected and the author sited stolen prescription forms as the source of the drug. In 1991, Strang again reported on the abuse of the 0.2 mg tablet that was being crushed and snorted. A rapid psychoactive effect was described. The DHHS document sited a recent buprenorphine-related death associated with smoking the crushed tablets. No data is presently available about the use or misuse of high-dose sublingual buprenorphine that was approved for addiction treatment in the U.K. in late 1999.

In France, the low-dose sublingual tablet for analgesia was first marketed in 1987 and abuse of this medication was identified soon after (Ardittiet al., 1992). By 1993, buprenorphine was the third most common drug associated with falsified prescriptions in southwestern France (Baumevieille et al , 1997). Since 1996, when high-dose sublingual buprenorphine for narcotic treatment was introduced in France, extensive abuse of buprenorphine has been reported. In 1998 a multidisciplinary task force reported that 12 to 31 % of addicts receiving buprenorphine treatment injected their medication and 2 to 9 % of buprenorphine users engaged in doctor-shopping receiving multiple prescriptions from more than one physician. In addition, buprenorphine was being abused as a "gateway" drug by younger individuals not yet addicted to narcotics. By 1999, buprenorphine was easily accessible on the illicit market in Paris and was selling for 10 to 15 francs (Dru, 1999). The most recent published report regarding buprenorphine use/abuse in France (Thirion et al., 2002) found that 12 % of buprenorphine patients get prescriptions from more than two doctors and 18 % have deviant maintenance treatment

(having multiple prescriptions from more than two doctors and/or obtaining more than 20 mg per day of buprenorphine).

In Scotland, extensive abuse of buprenorphine in combination with temazepam has been reported (Morrison, 1989; Sakol et al., 1989; Gray et al, 1989; Hammersely et al., 1990; Lavelle et al., 1991; Forsyth et al., 1993). In a study among drug abusers in contact with drug agencies in Glasgow (Hammersely et al., 1990), 93 % reported use of buprenorphine in the previous year with 90 % of those reporting frequent use (251 days out of 365 days) by injection. Among a group of non-dependent new drug abusers, 39% reported buprenorphine use with 5 % injecting. *The British Journal of Addiction* (1989, 84:1102) reported concern about the number of armed robberies of community pharmacies and wholesalers by individuals seeking buprenorphine in Scotland. This article reported that one firm was held up by four men, two armed with sawn-off shotguns, who stole 18,000 buprenorphine tablets and 200, 000 temazepam capsules. A 1992 study among 727 clients in a needle exchange program in Glasgow (Gruer et al., 1993), reported that the most frequently injected drugs were heroin (61 %) and buprenorphine (45 %) often combined with benzodiazepines.

In Ireland, O'Connor et al. (1988) reported that buprenorphine was a major drug of abuse among Dublin's opiate addicts. The authors reported extensive street availability and abuse by sublingual use, snorting or injecting. In addition, general practitioners reported that young patients were coming to their offices requesting buprenorphine as the only drug that "worked" for their dubious physical complaints. Forged prescriptions and pharmacy break-ins were additional sources for this drug.

In New Zealand, extensive intravenous abuse of the 0.2 mg buprenorphine tablet among opioid abusers led to the 1991 reformulation of buprenorphine to include 0.17 mg of naloxone. Robinson et al (1993) conducted two separate surveys among narcotic addicts presenting for treatment before and after the launch of the naloxone combination product. In 1990, 81 % of the patients reported intravenous buprenorphine abuse in the previous 4 weeks, 50 % reported exclusive use of buprenorphine and 65 % tested positive for the drug. In 1991, 57 % reported intravenous abuse of the combination tablet and 43 % tested positive for the combination. One third of the patients that used the combination product intravenously reported instances of withdrawal symptoms. The authors concluded that the combination product did act as a deterrent for some drug abusers but intravenous abuse of the combination product continued to be a significant problem among narcotic addicts.

In India, buprenorphine is relatively easy to get (often sold without a valid prescription), substitutes for heroin, produces significant addiction, and is viewed as a drug of high abuse potential (Basu et al., 1990; Bedi et al., 1998; Chowdhury et al., 1990; Singh et al 1986, 1992; Kumar, 1995). Government estimates of 50,000 buprenorphine abusers in Delphi alone account for 20 percent of opiate products abused in India since 1993 (Mudur, 1999). From January 1987 to April 1990, Sing et al. (1992) document 18 cases of buprenorphine dependence. All were abusing buprenorphine intravenously and all but one had previous narcotic abuse histories. The average daily doses were from

1 to 7 mg and were often combined with diazepam (30 to 100 mg). The withdrawal among these addicts was evaluated as about 50 % milder than heroin except the aches and pains continued for three to six weeks. In Napal, 78.4 % of a cohort (n=204) of intravenous drug abusers reported injecting buprenorphine (Chatterjee, 1996).

International trafficking data has been provided by Interpol and the United Nations International Narcotics Control Board (UN/INCB):

- 34,897 ampoules of buprenorphine were seized in Azerbaijan in route from India to the CIS countries in the Russian Federation. In the Russian Federation, four seizures of buprenorphine were made in 1996 and three in 1997.

- In India, the abuse of buprenorphine has been growing. In 1997 alone, six seizures of buprenorphine were made, the largest involving 43,350 ampoules. Indian authorities also reported seizures from tourists leaving the country. For example, in 1998, 2,900 ampoules of buprenorphine were found in the check-in luggage of a Georgian national leaving through the airport in Delhi.

- In Bangladesh, buprenorphine is reportedly abused by 90 % of the injecting drug abusers. Tidigesic injection ampoules are smuggled from India and seizures have continued to escalate with 757 ampoules in 1993 to 10,037 ampoules in 1997.

- In August 1998, 680 grams of buprenorphine were seized at the Moscow Airport in the bags of a traveler from New Delhi.

- November 1998, 7,520 tablets of buprenorphine were seized at the Oslo Airport from the luggage of a courier from Bangkok with a stop in Helsinki.

- The UN has reported abuse and/or seizures of buprenorphine in several other countries of the world including Denmark, Finland, France, Japan, Norway, Portugal, Mexico and Spain. In June of 1998, an attempt to divert an unspecified quantity of buprenorphine from China to Cambodia was thwarted by competent authorities of those countries and cooperation of the INCB.

- The INCB Reports for 1995, 1996 and 1997 urged the WHO to take prompt action to increase the international controls placed on buprenorphine siting significant trafficking from India to Bangladesh and Nepal as well as significant intravenous abuse contributing to the spread of AIDS.

Factor 5: The scope, duration and significance of abuse

Buprenorphine abuse was detected in many countries soon after it was approved for marketing. The initial profile of low abuse liability and high therapeutic index fueled decisions that allowed the marketing of buprenorphine without any significant restrictions or regulatory controls. Its easy accessibility and acceptability by a wide spectrum of drug abusers, including heroin addicts, resulted in its widespread abuse and a recommendation by the World Health Organization to have buprenorphine placed in Schedule III of the Psychotropic Convention. Surveys in several countries show that buprenorphine ranks among the top drugs most frequently abused (Lavelle et al., 1991; Arditti et al., 1992; Lapeyre-Mestre et al., 1997; Thirion et al, 1999; Shewan et al., 1998; Taylor et al., 1996; Coggans et al., 1991; Bernard et al., 1998). Austria, Australia, Germany, France, New Zealand, Norway and India have all increased the regulatory controls on buprenorphine as a consequence of significant abuse of this drug.

A number of factors have contributed to the illicit use of buprenorphine. In areas where heroin has been less available or of low quality, buprenorphine's low cost, easy accessibility, high purity and substantial euphoric effects have contributed to its popularity on the illicit market. Doctor shopping and forged prescriptions are important sources of this drug and large quantities of buprenorphine have been trafficked across international borders.

While extensive diversion, trafficking and abuse have been documented for both the sublingual tablets and injectable formulations, the sublingual tablet has a greater appeal to a wider range of drug abusers. The variety of routes of administration may account for this preference. The tablets can be abused by the sublingual route or they can be crushed and snorted or the powder can be solubilized and injected. Enhancement of absorption of the sublingual tablet can be accomplished by crushing the tablets, dissolving the buprenorphine in alcohol and administering the alcoholic solution sublingually.

Factor 6: What, if any, risk there is to the public safety.

Buprenorphine is a potent narcotic with high affinity for and slow dissociation from mu receptors. It has been shown to produce effects similar to other potent narcotics like hydromorphone including euphoria, pupillary constriction, respiratory depression and sedation. As a drug of considerable abuse potential, buprenorphine has been diverted, trafficked and abused by a wide segment of the drug abusing population from experienced drug abusers, including narcotic addicts, to inexperienced non-dependent initiates to drug abuse.

Abuse of high-dose sublingual tablets has been associated with severe respiratory depression and death as documented in France over the last five years. In contrast, controlled studies have found very few instances of severe respiratory depression associated with very high sublingual doses of buprenorphine. These controlled studies suggest that physicians and policy makers alike need not to be concerned with serious drug overdoses usually associated with that of heroin or other potent mu agonist pharmaceuticals. Indeed, when taken as prescribed (sublingually at therapeutic doses) without concomitant use of other CNS depressants, buprenorphine appears to have a high margin of safety. However, most of the deaths in France were associated with individuals who were not in comprehensive treatment programs and were injecting buprenorphine and other psychoactive drugs (particularly benzodiazepines). At the present level of control, there is every reason to believe that the same activity will occur in the U.S. if/when the new high-dose sublingual products become generally available through physician prescription.

Postmarketing data from France indicates that the use of buprenorphine among pregnant opiate-dependent women is associated with a neonatal abstinence syndrome. This withdrawal syndrome is mild to moderate in severity and the most common adverse event reported in France. Seven fetal deaths among mothers treated with Subutex® were reported.

The use of buprenorphine for the treatment of addiction in an office based setting is intended to expand treatment options for narcotic addicts. Increased availability of buprenorphine without appropriate controls, may, however, lead to abuse among young, non-addicted, drug abusers. Data from England, France, Scotland, and Ireland demonstrate that buprenorphine, if available, is abused by young, non-dependent drug abusers (Forsyth et al., 1993; Frischer, 1992; Hammerseley et al., 1990; O'Connor et al., 1988).

Factor 7: The drug's psychic or physiological dependence liability

Physical dependence on buprenorphine following chronic administration has been examined. Jasinski et al. (1978), first demonstrated that discontinuation of buprenorphine administration produced an abstinence syndrome that was delayed in onset with an extended duration. The withdrawal signs were similar to other narcotics and included anxiety, restlessness, muscle tension and pain, drug craving, irritability and increased sensitivity to pain. Peak withdrawal effects were not observed until about two weeks after the last dose of buprenorphine but were considered less severe than pure mu agonists like morphine or heroin. Other studies conducted by Kosten et al (1988), San et al. (1992) and Fudula (1990) found that abrupt discontinuation of buprenorphine produced a withdrawal syndrome characterized as mild to moderately severe in intensity that was delayed in onset and lasted for a protracted period of time.

(Kosten et al., 1990) examined the effects of opioid antagonists on patients maintained on 2 to 3 mg of buprenorphine for 30 days. The administration of oral

naltrexone (1 mg) had no effect but 35 mg iv naloxone produced significant withdrawal signs, though of less intensity than that of methadone patients maintained on 36 mg/day who were administered 1 mg of naltrexone. In another study, Eissenberg et al.(1996), subjects were maintained on 8 mg of sublingual buprenorphine. Low doses of naloxone (0.3 and 1.0 mg) did not precipitate withdrawal signs, but 3 mg of oral naltrexone or 3 and 10 mg of IM naloxone produced significant narcotic withdrawal signs. These studies demonstrated that high doses of narcotic antagonists are needed to produce significant, but less intense withdrawal signs (compared to the withdrawal syndrome of pure mu agonists) in buprenorphine-maintained clients.

In a buprenorphine street-addict population, Sing et al (1992) reported that the withdrawal from buprenorphine was about 50 % less severe than heroin but the aches and pains continued for three to six weeks. In addition, postmarketing data from France indicates that the use of buprenorphine among pregnant opiate-dependent women is associated with a neonatal abstinence syndrome. This withdrawal syndrome is mild to moderate in severity and the most common adverse event reported in France.

The subjective effects produced by buprenorphine (i.e. recognized as morphine or heroin-like by experienced drug abusers) and the extent of illegal activities engaged in by abusers in order to obtain buprenorphine (if, in fact, the illegal activities are a result of drug craving as has been reported by many buprenorphine abusers) suggest that buprenorphine use is associated with high psychological dependence.

Factor 8: Whether the substance is an immediate precursor of a substance already controlled

Buprenorphine is not an immediate precursor to any controlled substance.

Findings:

After consideration of the eight factors contained herein and the scientific and medical evaluation and scheduling recommendation made by the DHHS, the DEA finds that buprenorphine meets the definition of a Schedule III narcotic substance under 21 U.S.C. 812(b):

1. **Buprenorphine has a potential for abuse less than the drugs or other substances in Schedule I or II.**

Buprenorphine is classified as a long-acting partial agonist with a high affinity for and slow dissociation from the mu-opioid receptors. Buprenorphine produces effects similar to other potent mu agonists including euphoria, drug liking, respiratory depression pupillary constriction and sedation and is recognized as morphine or heroin-like by experienced narcotic abusers. Significant abuse of buprenorphine has been reported in many countries. Buprenorphine products have been diverted from legitimate channels through theft; doctor shopping and fraudulent prescriptions and significant amounts of buprenorphine have been seized by law enforcement authorities in other countries. These data suggest that buprenorphine closely resembles other narcotics in Schedule II.

However, buprenorphine effects are less dose-dependent than pure mu agonists and a "ceiling effect" has been demonstrated for many of the actions of buprenorphine. This attenuation in effects at high doses may have a blunting effect on the continued escalation in dose to obtain greater effects. Buprenorphine is also a safer drug in overdose than other Schedule II substances despite the many deaths that have been reported from France. Therefore, buprenorphine appears to have somewhat less abuse potential than Schedule I or II substances but more abuse potential than similar drugs in Schedule IV.

2. **Buprenorphine has a currently accepted medical use in treatment in the United States.**

Buprenorphine (Buprenex®) is approved for use as a parenteral narcotic analgesic. Two new sublingual buprenorphine products (Subutex and Suboxone) for the treatment of narcotic addiction have received approvable letters fro ⊿ FDA and are likely to receive marketing approval in 2002.

3. **Abuse of buprenorphine may lead to moderate or low physical dependence or high psychological dependence.**

Data from a number of studies indicate that chronic use of buprenorphine is associated with a withdrawal syndrome that is of less intensity and, often, of longer duration than other mu opioid agonists in Schedule I or II. The withdrawal effects has been characterized as mild to moderate in severity. Buprenorphine abuse and addiction have been reported in many countries. Discontinuation of buprenorphine abuse has been associated with drug craving and in some patients has resulted in the resumption of

heroin (or other narcotic) abuse. Buprenorphine can substitute for heroin and is thought to have a similar psychological dependence profile.

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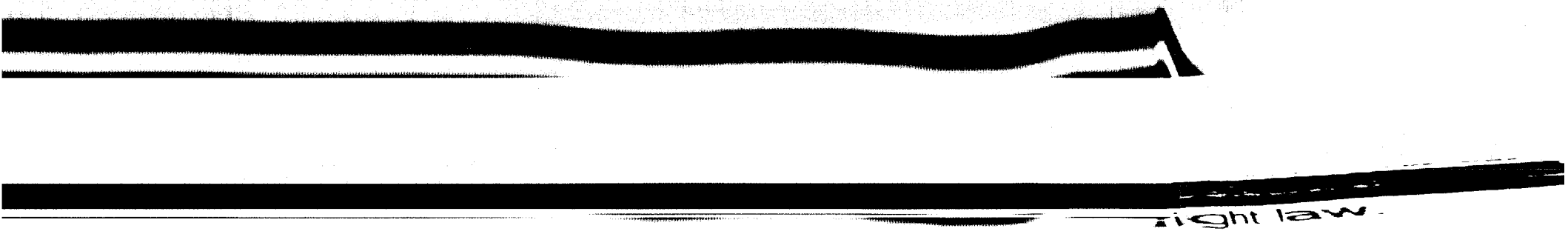
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Deaths involving buprenorphine: a compendium of French cases

P. Kintz*

Institut de Médecine Légale, Universite Louis Pasteur (ULP), 11 rue Humann, 67000 Strasbourg, France

Abstract

Buprenorphine at high dosage became available in France in 1996, as a substitution treatment for heroin addicts. Since this date, numerous deaths were attributed to this drug. This paper reports two original series of 39 and 78 fatalities involving buprenorphine observed at the Institute of Legal Medicine of Strasbourg and at 13 other French forensic centers, respectively. The files were recorded from January 1996–May 2000. The first 20 fatalities that were previously published were excluded from this epidemiological study. From these 117 subjects, 96 were male (82%). Buprenorphine and its primary metabolite norbuprenophine were assayed in post-mortem blood by HPLC/MS (n = 11 labs) or by GC/MS (n = 3 labs). Blood levels for buprenorphine ranged from 0.5 to 51.0 ng/ml (mean 10.2 ng/ml) and 0.1 to 76 ng/ml (mean 12.6 ng/ml) in Strasbourg and the other centers, respectively. Blood levels for norbuprenorphine ranged from 0.2 to 47.1 ng/ml (mean 8.2 ng/ml) and <0.1 to 65 ng/ml (mean 10.6 ng/ml) in Strasbourg and the other centers, respectively. The mean values appear to be within the therapeutic range. Buprenorphine was identified in 24 of the 26 hair samples assayed in Strasbourg, at concentrations ranging from 10 to 1080 pg/mg. Intravenous injection of crushed tablets, a concomitant intake of psychotropics (especially benzodiazepines and neuroleptics) and the high dosage of the buprenorphine formulation available in France appear as the major risk factors for such fatalities. In addition, two suicide-related deaths were also observed, with blood buprenorphine concentrations at 144 and 3276 ng/ml.

Keywords: Buprenorphine; Poisoning; Fatality; Substitution program

1. Introduction

Buprenorphine is a semisynthetic opioid derivative, closely related to morphine which is obtained from thebaine after a seven-step chemical procedure. At low doses (typically 0.3–0.6 mg intravenous or intramuscular), buprenorphine is a powerful analgesic, 25–40 times more potent than morphine, with mixed agonist/antagonist activity on central receptors. The drug is a partial mu receptor agonist and a kappa receptor antagonist. It shows a very slow dissociation from opiate receptors and consequently has a duration of action of at least 24 h. Buprenorphine is weakly antagonized by naloxone [1,2].

Buprenorphine is characterized by a weak oral bioavailability and low therapeutic concentrations, owing to its high lipid solubility. Its main metabolite is desalkyl-buprenorphine or norbuprenorphine and both drugs are glucuroconjugated.

Following a single 0.4 mg sublingual dose, Bullingham et al. reported plasma concentrations of buprenorphine in the range 0.45 to 0.84 ng/ml [3]. According to Kuhlman et al. [4], average peak plasma concentrations of 3.31 ng/ml (range 1.93–7.19 ng/ml) and 1.98 ng/ml (range 0.25–3.90 ng/ml) were observed for buprenorphine in six subjects given 4.0 mg sublingual and buccal, respectively.

Under the tradename Temgesic® at dosages of 0.2 mg, buprenorphine has been widely prescribed for about 20 years for the treatment of moderate to severe pain as well as in anaesthesiology for the premedication and/or anaesthetic induction.

More recently it has been also recognized as a medication of interest for the substitutive management of opiate-dependent individuals. Under the tradename Subutex®, a high-dosage formulation (0.4, 2, and 8 mg tablets for sublingual use) is available in France since February 1996 in this specific indication. Contrary to methadone, delivered on a daily basis in specific centers and continuous survey of the patient by urine analysis achieved each week, Subutex® may be ordered by any physician up to 28 days, and is supplied by any pharmacist. Patients are not entailed to take

* Tel.: +33-388-249-126; fax: +33-388-240-085.
E-mail address: pascal.kintz@wanadoo.fr (P. Kintz).

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the drug in presence of the physician or pharmacist. Urine controls are not mandatory, and in practice are almost never realized.

Today, this drug is largely used in France for the treatment of about 60 000 heroin addicts, but can also be easily found on the black market.

From a general point of view, this substitution program can be considered as successful. The number of fatal heroin overdoses has dramatically dropped during the last years, from about 500 cases per year to less than 100 in 1999.

However, since the first buprenorphine fatality observed by Tracqui et al. [5] in August 1996, several cases were recorded by the French toxicologists. In 1998, Tracqui et al. [6] published a series of 20 fatalities collected from five centers. In all cases, a concomitant intake of psychotropics (mostly benzodiazepines) was observed.

Besides other sources of information (drug enforcement services, customs, intensive care units, etc.), the epidemiological data collected from forensic toxicologists may be of value to follow the evolutions of narcotic deaths in the course of time.

This paper presents the results of a new retrospective survey on buprenorphine-related deaths in the region of Strasbourg from March 1998–July 2000 and from 13 different forensic centers of France from mid 1996–March 2000.

2. Materials and methods

2.1. Subjects

Thirty nine from about 1200 postmortem examinations at the laboratory of toxicology from the Institute of Legal Medicine of Strasbourg were positive for buprenorphine in blood during the mentioned period. Hair specimens were available in 26 cases. In all cases, autopsies revealed signs of asphyxia (cyanosis, multivisceral congestion, pulmonary oedema, etc.) but showed no signs of violence. No other cause of death could be established by experienced pathologists.

Data from other centers were obtained through a question from the Forum of discussion of the Internet web of the French Society of Analytical Toxicology (SFTA, www.sfta.org). Toxicologists were asked to give their observations about buprenorphine-related deaths. Only cases where the cause of death was listed as due to buprenorphine intoxication (consistent with the findings of the autopsy and Police records) alone or in combination were included in the study. Seventy eight fatalities were documented in 13 different centers. These centers were located in Paris (two centers), Grenoble, Bordeaux, Le Havre, Lille (three centers), Angers, Poitiers, Luxembourg, Limoges and Montpellier.

2.2. Toxicological analyses

In Strasbourg, buprenorphine and norbuprenorphine were assayed in post-mortem blood by using an HPLC/MS procedure described elsewhere [7]. Briefly, 3 ml blood were extracted at pH 8.4 by 5 ml of chloroform/2-propanol/*n*-heptane (CPH) (25:10:65, v/v) after addition of 15 ng of buprenorphine-d_4 and norbuprenorphine-d_3 (Promochem, Molsheim, France). After agitation and centrifugation, the organic phase was removed. After evaporation, dry extracts were resuspended in 25 µl methanol, from which 5 µl were injected onto a 4 µm NovaPak (Waters, Milford, MA) C18 column (150 mm × 2.0 mm, i.d.).

Hair strands (approximately 100 mg) were twice decontaminated in 5 ml of methylene chloride, for 2 min at room temperature. Hair strands were pulverized in a ball mill and 50 mg of powdered hair were incubated in 1 ml 0.1 N HCl, overnight at 56°C, in presence of 15 ng of deuterated standards, buprenorphine-d4 and norbuprenorphine-d_3. After neutralization with NaOH, the solubilization medium was extracted using 5 ml of the same ternary solvent, followed by the same extraction process as for blood.

Reversed-phase separation was achieved in 10 min, using a linear gradient of acetonitrile (ACN)/2 mM NH_4COOH buffer, pH 3.0 (ACN 50–85% in 10 min). The detection was carried out on a Perkin-Elmer Sciex (Foster City, CA) API-100 mass spectrometer equipped with a pneumatically assisted electrospray (Ionspray™, Perkin-Elmer Sciex) interface. The ion sampling orifice was held at +75 V and the electromultiplier at +2700 V. MS data were collected in single ion monitoring at *m/z* 414 and 417 (norbuprenorphine and norbuprenorphine-d_3) and 468 and 472 (buprenorphine and buprenorphine-d_4). Under these analytical conditions, the limits of quantitation for buprenorphine and norbuprenorphine in blood were 0.2 and 0.1 ng/ml, respectively.

In addition to buprenorphine specific analysis, a complementary screening of the post-mortem blood was performed in all subjects using fluorescence polarization immunoassay (FPIA) on the Abbott ADx™, UV spectrophotometry (carbon monoxide), GC/FID (meprobamate, ethanol), head-space GC/NPD (cyanides), head-space GC/MS (usual organic solvents) and LC/DAD + GC/MS (pharmaceuticals, drugs of abuse).

Other centers used either GC/MS (3 labs) or LC/MS (10 labs) to test for buprenorphine, according to their own validated procedure [8,9].

3. Results

Generally, when interpreting a blood concentration from a postmortem case, the toxicologist can find helpful informations in databases presenting therapeutic, toxic and lethal concentrations. Unfortunately, there is quite no suitable references in the literature, that is very poor for buprenorphine. At best, therapeutic concentrations can be evaluated from clinical studies in the range 2–20 ng/ml [10]. No toxic nor lethal concentrations are available, as this drug seems to be a typical French problem. Due to this situation, Tracqui et al. [6] attributed 20 fatalities to buprenorphine poisoning,

Table 1
Toxicological data in 39 fatalities observed in Strasbourg

Buprenorphine concentrations in blood	0.5–51.0 ng/ml, mean: 10.2 ng/ml
Norbuprenorphine concentrations in blood	0.2–47.1 ng/ml, mean: 8.2 ng/ml
Buprenorphine + EtOH + various	10 cases (25.6%)
Buprenorphine + benzos	31 cases (79.5%)
Buprenorphine + neuroleptics	18 cases (46.2%)
Buprenorphine + other psychotropics	8 cases (20.5%)
Buprenorphine + narcotics	3 cases (7.6%)
Buprenorphine + cocaine	0 case
Buprenorphine + cannabis	22 cases (56.4%)

Table 2
Toxicological data in 78 fatalities observed in 13 French centers

Buprenorphine concentrations in blood	0.1–76.0 ng/ml, mean: 12.6 ng/ml
Norbuprenorphine concentrations in blood[a]	<0.1–65.0 ng/ml, mean: 10.6 ng/ml
Buprenorphine + EtOH + various	24 cases (30.8%)
Buprenorphine + benzos	60 cases (76.9%)
Buprenorphine + neuroleptics	19 cases (24.3%)
Buprenorphine + other psychotropics	16 cases (20.5%)
Buprenorphine + narcotics	20 cases (25.6%)
Buprenorphine + cocaine	6 cases (7.7%)
Buprenorphine + cannabis	36 cases (46.2%)

[a] Norbuprenorphine was measured in only 61 cases.

even at therapeutic concentrations, as no other cause of death was obvious. These authors concluded that buprenorphine can be life-threatening without overdosage, when associated to psychotropic drugs.

Recent results, collected both in Strasbourg and several other centers confirm these preliminary findings. Toxicological data are reported in Tables 1 and 2

Blood levels for buprenorphine ranged from 0.5 to 51.0 ng/ml (mean 10.2 ng/ml) and 0.1 to 76 ng/ml (mean 12.6 ng/ml) in Strasbourg and the other centers, respectively. Blood levels for norbuprenorphine ranged from 0.2 to 47.1 ng/ml (mean 8.2 ng/ml) and <0.1 to 65 ng/ml (mean 10.6 ng/ml) in Strasbourg and the other centers, respectively.

From these 117 subjects, 96 were male (82%), most of them with a low socio-professional status. Circumstances of death were strongly suggestive of a drug fatality in about 2/3 of subjects: empty packages of Subutex® and/or remains of buprenorphine (in spoons, straws, etc.), other psychotropics (pharmaceuticals or drugs of abuse) or used syringe(s). Evidence of violence was never found at autopsy, but all corpses presented the features of a prolonged asphyxiation (deep cyanosis, multivisceral congestion, pulmonary oedema). These signs are very usual in all deaths involving CNS depressants, especially in opiate-related fatalities. Needle marks suggesting recent i.v. injection(s) were observed in about half of the subjects.

Table 3
Typical fatalities observed in Strasbourg

Data	Buprenorphine in blood (ng/ml)	Norbuprenorphine in blood (ng/ml)	Other compounds in blood
Woman, 21-year-old, found in her bed, needle marks	3.3	1.4	Bromazepam: 304 ng/ml; nordiazepam: 1060 ng/ml; ethanol: 0.18 g/l
Man, 32-year-old, found at the home of a friend, under substitution	3.7	1.5	Bromazepam: 106 ng/ml; nordiazepam: 1510 ng/ml; cyamemazine: 314 ng/ml
Man, 22-year-old, found in the street, homeless, under substitution	2.6	1.8	Nordiazepam: 6540 ng/ml; meprobamate: 83 mg/l; THC–COOH: 0.9 ng/ml
Woman, 30-year-old, found at home, no prescription of Subutex®	7.5	14.9	Nordiazepam: 5020 ng/ml; 7-amino-flunitrazepam: 56 ng/ml
Man, 28-year-old, known to be an opiate addict, needle marks	8.7	5.3	Fluoxetine: 301 ng/ml; cyamemazine: 421 ng/ml; ethanol: 0.32 ng/ml; 7-amino-flunitrazepam: 96 ng/ml

Buprenorphine was also detected in 24 of the 26 hair samples assayed in Strasbourg, showing a chronical use of the drug for the individuals concerned. Concentrations ranged from 10 to 1080, and not detected to 1020 pg/mg for buprenorphine and norbuprenorphine, respectively.

Five typical cases, observed in Strasbourg, are detailed in Table 3.

Beside these 117 cases, 2 other cases were observed, being classified as suicide, with buprenorphine blood concentrations of 144 and 3276 ng/ml [11].

4. Discussion

Fatalities involving buprenorphine alone seem very unusual: in these series, all cases but one involved a concomitant intake of psychotropics. In this unique case, the cause of death was listed as tracheobronchial inhalation (Mendelsson' syndrome). The blood buprenorphine concentration was 0.8 ng/ml. Benzodiazepines ranked first in association, since they were present in 91 observations (from which 64 with nordiazepam). The role of associated benzodiazepines had been previously emphasized in several clinical reports of severe, nonfatal respiratory depressions observed when giving buprenorphine to anesthesized patients [12]. It is suggested that the CNS-depressant effects of buprenorphine may be synergically potentialized by some benzodiazepines (otherwise almost harmless if taken alone). Similar interactions probably exist between buprenorphine and other psychotropics, such as neuroleptics and antidepressants. Among the neuroleptics (37 cases), cyamemazine was present in 26 cases. Antidepressants (18 cases) were tricyclic (8 cases) or serotonin reuptake inhibitors (10 cases). A concomitant intake of other narcotics was observed in 23 cases, mostly outside the region of Strasbourg. These narcotics included morphine (12 cases with 8 at toxic concentrations), codeine (2 cases), methadone (4 cases), pethidine (1 case) and propoxyphene (4 cases). A fatal association involving ethanol and buprenorphine was observed in 4 cases, with the following concentrations: 0.8 and 2.18, 1.3 and 0.73, 11.4 and 0.4, and 18.0 ng/ml and 2.29 g/l for buprenorphine and ethanol, respectively. Such cases were not observed previously.

Injecting buprenorphine intravenously after crushing the sublingual tablets probably constitutes another risk factor of potentially fatal overdosage. Most of the clinical reports of buprenorphine-induced respiratory depression concern intravenous administration [13]. This way of administration involves a quasi-instantaneous saturation of the central opiate receptors and a maximization of buprenorphine bioavailability, which is otherwise poor, especially per os (20–30%).

Finally, the high dosage of Subutex® tablets is also likely to play a role in the occurrence of accidents, in spite of a theoretical 'ceiling effect' (related to the agonist/antagonist duality of buprenorphine pharmacodynamic activity) claimed to reduce this risk [14].

5. Conclusion

This paper has presented an original compendium of 117 fatalities attributed to buprenorphine overdosage that completes the 20 first cases previously observed and recorded in France since the introduction of a high-dosage formulation devoted to the substitution of opiate addicts. This seems to be a specific French problem, as no other deaths were reported anywhere else.

The risks incurred by the misuse of buprenorphine seem to arise through a combination of two practices: (1) association of other psychotropics, especially benzodiazepines and neuroleptics, and (2) improper use of the tablet form for intravenous administration or massive oral doses. The demonstration of potentially lethal effects of the buprenorphine–psychotropic(s) association challenges the purported harmlessness of buprenorphine. The total number of buprenorphine-related fatalities in France is probably largely underestimated due to: (1) the drug is difficult to analyze (low concentration, no immunoassay in France); (2) only some forensic centers responded to the question; and (3) in numerous place, in case of obvious overdose (known drug addict, presence of a syringe or packages of Subutex®), no autopsy is requested by the Police or a judge.

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Cases of buprenorphine abuse in India

Singh RA, Mattoo SK, Malhotra A, Varma VK. Cases of buprenorphine abuse in India.
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R. A. Singh, S. K. Mattoo, A. Malhotra, V. K. Varma

Drug De-addiction and Treatment Centre, Department of Psychiatry, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Buprenorphine was introduced as a potent analgesic with low abuse potential. Reports of buprenorphine abuse by opiate abusers have accumulated over the years, highlighting its use as a cheap alternative to heroin. The lower potency compared with heroin is being compensated by using a cocktail of buprenorphine with benzodiazepines or cyclizine. This study of 18 cases seen over 3 years broadly confirms these findings. Four cases reported haematemesis during acute withdrawal, a symptom not reported in earlier studies.

Key words: buprenorphine; diazepam; drug abuse

Dr. S.K. Mattoo, M.D., Department of Psychiatry, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India

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Buprenorphine is a mixed agonist-antagonist opioid available in sublingual, oral and parenteral preparations. As an analgesic it is 25 to 40 times more potent than morphine (1). Nevertheless, it has a lower overdose lethality (2), milder euphoric effects and mild and delayed withdrawal symptoms (3,4). Hence, it was claimed to be a safe opiate analgesic with low abuse potential (3).

Challenging this claim, the first report of buprenorphine abuse came from New Zealand (5). In subsequent reports, abuse by the oral as well as parenteral routes was implicated (6–17) and the concurrent abuse of cyclizine or temazepam (12–17) purportedly enhanced the euphoriant effect of buprenorphine (15–17). Almost all the studies reported buprenorphine abuse as a substitute among opiate, mainly heroin, addicts.

In India, buprenorphine became available in 1986 as a prescription drug. From 1987 to 1990, our centre has recorded a gradual increase in the number of cases of buprenorphine dependence. All cases were using buprenorphine intravenously. An initial report of 3 cases, the first such report from India, has already been published (9). This study deals with findings among all the buprenorphine cases seen so far.

Material and methods

The Department of Psychiatry at the Postgraduate Institute of Medical Education and Research, Chandigarh, India, has been running a deaddiction clinic since 1978. The clinic was upgraded to a de-addiction and treatment centre in 1988 under the drug control programme of the Government of India. The centre receives the cases on the basis of self, family or case-to-case referral or from other medical or non-medical agencies. The cases are first seen in the general psychiatric clinic, which gives them an appointment for the de-addiction clinic and medical attention in the intervening period of 1–2 weeks. The de-addiction centre services include outpatient and inpatient programmes of detoxification and psychosocial intervention by a team of psychiatrists, clinical psychologists and social workers. The follow-up comprises regular outpatient visits and, in case of a missed appointment, 2 call letters and/or a home visit by a social worker for the local city patients.

Over the last decade we have registered a gradual increase in the cases of dependence on heroin and other synthetic opiates. The first case of buprenorphine dependence was registered in 1987. This report is based on 18 cases of buprenorphine dependence (of 107 cases of opiate dependence) seen between January 1987 and April 1990. All the 18 cases were abusing buprenorphine intravenously and in 11 cases buprenorphine was being used as a buprenorphine-diazepam cocktail. All the cases were re-examined by either of the first two authors to obtain detailed information about the drug abuse. Urine analysis for opiates could not be carried out, as the facilities were not available.

Results

All 18 cases were men from 19 to 37 years old (mean age 26 years); half were married and other half unmarried; 16 were from urban areas; 14 cases had completed school; 9 cases had never held any occupation; all the 9 employed cases had a middle or lower occupational status; the head of the family

was the father in 12 cases, mother in 2 cases and self in 4 cases.

All the cases, except one, were abusing other opioids and/or other drugs before abusing buprenorphine. Concurrent abuse was mainly of alcohol and cannabis, while the common substances of past abuse were heroin, cannabis, alcohol and opium.

The total duration of opioid abuse varied from 2 to 12 years (mean 5 years); the duration of buprenorphine abuse varied from 4 to 36 months (mean 14 months). The daily doses varied from 1 to 7 mg (mean 3 mg) for buprenorphine and from 30 to 100 mg (mean 60 mg) for diazepam. The common pattern of usage was 3 to 4 intravenous doses daily of 0.6 mg buprenorphine, with or without 10 to 20 mg diazepam, self-injected at 4- to 8-h intervals. Although 4 cases were using the drug in group setting only, others were using the drug either in group setting or when alone. All cases were using disposable needle-syringe sets, each set being used for 3 to 6 days, rinsed with tap-water after each use. Ten cases reported having shared their syringes or needles with their group-mates at some time or the other.

Of 3 concurrent heroin users, 2 reported much less euphoria with heroin than with the period of heroin use before abusing buprenorphine. The use of buprenorphine had been picked up from the fellow-addicts ($n = 12$) and medical practitioners ($n = 6$). The reasons for starting buprenorphine were non-availability of heroin ($n = 10$), to decrease the intake of heroin ($n = 14$) and low cost ($n = 3$). The daily expenses on buprenorphine (with or without diazepam) abuse were 4 to 6 times less than for heroin abuse.

The buprenorphine-diazepam cocktail was described to be more enjoyable than buprenorphine alone in terms of the "kick" being more intense ($n = 4$) and more rapid in onset or longer lasting or both ($n = 7$). The cocktail effects were reported to last for 45–180 min *vs* 30–45 min for buprenorphine alone.

Aches and pains, insomnia, nasal symptoms, irritability and restlessness were the most frequent withdrawal symptoms reported; muscle twitching, diarrhoea and palpitation were least frequent.

The general reporting of withdrawal severity was "50% milder than heroin". The withdrawal was reported (and also observed in 9 hospitalized cases) to start 1–2 days after the last dose, peak at 2 to 3 days and subside by 15–20 days, except for aches and pains, which lasted for 3–6 weeks. A remarkable symptom reported during the acute withdrawal in 4 cases was haematemesis; 2–5 ml of fresh blood, up to 3 times a day. In 2 such hospitalized cases the endoscopic examination revealed gastric antral erosions.

The detoxification was carried out in the outpatient department and in the wards (9 cases each). In all cases the patient and/or the family were given counselling about drug and opiate abuse and its management, including guidance about such specific problems as interpersonal or occupational difficulties. Nine cases were detoxified with clonidine; others were detoxified under substitution with meperidine or morphine.

The follow-up data are based on regular appointments and special appointment through a call letter, for the purpose of this study. The details of the follow-up showed that about three fourths of the cases were lost by 3 visits or by 1 year. The drug abuse status at the last follow-up visit showed that 8 cases were abstaining and 10 cases had restarted buprenorphine or heroin (5 cases each). Of the 5 cases restarting buprenorphine, compared with pre-treatment daily dose, 2 cases were using lower doses and 3 cases were using the same or higher doses.

Discussion

Compared with Ireland, where buprenorphine abuse was reported about 6 years after its introduction (16), in India the lag period was only 1 year. However, the increase in the number of abusers among the opiate abusers was not as rapid at our centre. This may be due to the overall lower prevalence of abusers of hard drugs or more stringent legal provision against opiates.

Almost all cases graduated to buprenorphine from heroin and 14 of 17 cases shifted either due to non-availability of heroin or to decrease the heroin consumption, confirming the earlier reports that buprenorphine is abused not as the preferred drug but as an alternative to heroin. The preference of the buprenorphine-diazepam cocktail abuser for the cocktail over buprenorphine alone confirms the earlier subjective patient reports that buprenorphine has a low euphoriant effect and that cocktail with temazepam or cyclizine enhances this effect (15–17). The preference for intramuscular route reported by the 2 other Indian studies (10, 11) is in contrast to our findings and cannot be explained. The partial opiate-antagonistic effect of buprenorphine is confirmed by some though not all of the cases reporting decreased euphoria with concurrently used heroin.

That all the cases, except for one, had started the drug abuse career with drugs other than buprenorphine suggests its low prescription in general practice. This is also supported by the fact that all the 6 cases initiated to buprenorphine by the medical practitioners were exposed to substitution withdrawal therapy for opiate dependence. The same was true for all fellow addicts who initiated some of our cases to buprenorphine.

Two strong reasons for the continued use of buprenorphine seem to be its availability through legal channels and its being cheaper than heroin (16). The withdrawal symptoms, as reported and as observed in the hospitalized cases, were milder than after heroin. But the onset of withdrawal syndrome was not delayed by about 2 weeks, as expected according to pharmacological studies (3, 4).

In 9 hospitalized cases the laboratory investigations (haemogram, urine-routine examination, liver function tests and human immunodeficiency virus test) revealed no abnormality. An occasional and mild haematemesis as a part of withdrawal syndromes has not been reported earlier. In our cases reporting haematemesis, the history and examination suggested no other physical pathology to explain the symptom.

The follow-up shows generally poor outcome and an early drop-out, though the cases followed-up for more than 6 months were more often abstaining or had reduced the intake. Of the 10 cases restarting opiate-abuse, 5 had reverted back to heroin, indicating the greater euphoriant and abuse potential of heroin.

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The Times of India

Wednesday, August 16, 2000

Chemists selling illegal drugs to be booked

Lalit Kumar

NOIDA: The Noida police will book under the Narcotic Drugs and Psychotropic Substance Act any chemists who sell potentially lethal narcotics and tranquillisers without proper prescriptions.

The decision follows the death of a domestic help, Pritam Singh, in Sector 30. The death appears to have been due to an overdose of buprenorphine injections.

Gautam Budh Nagar police chief Anand Kumar told The Times of India News Service that a search was on to trace the chemist who sold the synthetic opiate to Pritam Singh. Two vials of the injection were found among his belongings.

As reported earlier, buprenorphine addiction is on the rise in Noida. Singh's death appears to establish that the economically weaker sections are also becoming addicted to the drug also known as Norphin or Tidigesic.

Meanwhile, according to prominent Noida physician and local Indian Medical Association unit vice-president Dr Sukhendu Roy Pritam Singh's death is being taken "very seriously".

"We will speak to the district chief medical officer very soon. And we will jointly decide what steps can be taken against chemists selling such drugs without prescriptions," he said.

Dr Roy said buprenorphine tends to cause respiratory depression (stoppage of breathing) in certain patients. It can also heighten the effects of other drugs used alongside.

District CMO Dr Vinod Kumar has promised action against the offending chemists.

---- INDEX REFERENCES ----

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Drugscope News

Buprenorphine prescription withdrawn in Norway

Hassela Nordic Network reports that from 1 October Norway's private practitioners will no longer be able to prescribe buprenophine to heroin addicts.

Norway's Minister of Social affairs, Guri Ingbrigtsen, says the change has been due for a long time as these substances have been prescribed carelessly by many doctors and then sold illegally on the streets.

The Ministry would instead like to see heroin-addicts in the government funded methadone programme, where an individual treatment plan is drawn up for each person.

The problem is that there are already more than 800 people waiting to get into the programme and it is not accessible for a majority of the country's 12,000 heroin addicts.

Recently the methadone programme received an additional NKr 35 million. According to Guri Ingbigtsen, this sum will double the possibilities for addicts to be admitted to the programme and will cover the needs of next year.

One doctor who regularly prescribes buprenophine medication to heroin addicts, Roger Gundersen, is disappointed by the government's decision. He says that these medications, for example Subutex and Temgesic, enable his patients to stay off drugs and provide a start for rehabilitation. Nevertheless he sees a possibility to continue prescribing Subutex to most of his patients, as the medication may be prescribed to patients with chronic pain and most of Gundersen's heroin addicted patients do suffer from chronic pain.

Full story at Hassela Nordic Network

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PHARMACEUTICALS: RESTRICTIONS IN USE AND AVAILABILITY

March 2001

Essential Drugs and Medicines – Quality Assurance and Safety of Medicines
Health Technology and Pharmaceuticals
World Health Organization
Geneva, Switzerland

PHARMACEUTICALS:
RESTRICTIONS IN USE AND AVAILABILITY

Prepared within the context of the United Nations publication

"Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments"

Update of the Sixth Issue – March 2001

Essential Drugs and Medicines – Quality Assurance and Safety of Medicines
Health Technology and Pharmaceuticals
World Health Organization
Geneva, Switzerland

This text is the second update to the Sixth Issue of the United Nations Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments - Pharmaceuticals (UN General Assembly Resolutions 37/137, 1982; 38/149, 1983; 39/229, 1984; 44/226, 1989). It is offered as a service to drug regulators, the pharmaceutical industry, and to everyone interested in assuring the safe and rational use of drugs. It complements and consolidates other drug-related information issued by the World Health Organization, including the WHO Rapid Alerts, WHO Pharmaceuticals Newsletter and the quarterly subscription journal WHO Drug Information.

Scope and presentation

This volume presents information on new national regulatory decisions, and on voluntary withdrawal of products by manufacturers on grounds of safety, that were reported to WHO up to December 2000.

Products are listed alphabetically within sections; International Nonproprietary Names (INNs) have been used whenever possible. Each product entry includes, where available, the Chemical Abstracts Service registry number (CAS number); synonyms including other generic names and chemical names; the effective date on which the regulation came into force; a summary of regulatory measures taken by governments; brief explanatory comments where necessary; and legal and bibliographical references.

While the information cannot be regarded as exhaustive, either in terms of products or regulatory measures, it covers regulatory actions taken by a total of 41 governments on 76 products. It should be noted, none the less, that decisions taken by a limited number of governments on a specific product may not be representative of the positions of other governments. Moreover, the fact that a given product is not listed as regulated by a country does not necessarily mean that it is permitted in that country; it may mean that the relevant regulatory decision has not been communicated to WHO or that the product has not been submitted for registration. The efficacy of products listed is not addressed, but is an aspect that may be crucial when a government is considering regulatory action.

Criteria for the inclusion of products in the Consolidated List (see next page) were developed in 1985 and revised in the light of the comments received from governments. However, governments' interpretation of the criterion "severely restricted", in particular, continues to vary widely, leading to considerable unevenness in reporting. When necessary, additional information and/or clarification has been requested from governments; products which clearly do not meet the criteria have been omitted after consultation with governments. Information received from non-governmental organizations has, in each case, been verified with governments.

The information provided also includes references to relevant legal or statutory documents that enable the user to ascertain the legal context and scope of the regulations. Such references cannot be given for most entries relating to specific pharmaceutical products since the relevant licences are often made or amended by an administrative decision which is not published. Brief explanatory comments also appear, where necessary, to clarify certain regulatory actions and put them into broader context.

Criteria for the inclusion of pharmaceutical products in the UN Consolidated List

a) ***Banned product***

A product that has been withdrawn from use and/or sale nationally in one or more countries by order of the competent national authority, having regard to its safety in relation to its intended use.

b) ***Voluntary withdrawal***

A product that has been withdrawn from use and/or sale nationally in one or more countries by voluntary action of the manufacturer, having regard to its safety in relation to its intended use.

c) ***Severely restricted***

A product containing:

(i) a substance that is controlled more rigorously than is provided for under the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances or that is subject to analogous control at the national level before it has been considered for international scheduling.

(ii) a substance that may be incorporated in pharmaceutical dosage forms only within the specific limits determined by statute.

(iii) a substance that is approved by a competent national authority and is subjected to restrictions that exclude its use in a substantial proportion of the potential target population of patients having regard to its safety. A substance which from the outset has been severely restricted in its indications having regard to the known balance of safety and efficacy is excluded.

d) ***Not approved***

A product that has been formally submitted for registration by a manufacturer to a national competent authority and which has been rejected on grounds of safety.

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Product name: **Alatrofloxacin mesilate**

CAS number: **157605-25-9**

Synonyms: 7-{(1R,5S,6s)-6-[(S)-2-Aminopropionamido)propionamido]-3-azabicyclo[3.1.0]hex-3-yl}-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulphonate

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	The Drug and Medical Technology Agency have rejected registration of alatrofloxacin because recent studies have shown serious and unpredictable liver injuries after administration of the drug. (Reference: Communication to WHO, 9 August 2000)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has not approved alatrofloxacin since it is associated with hepatic adverse reactions. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Aldesleukin**

CAS number:

Synonyms: Interleukin-2; Epidermal thymocyte Activating Factor; T-cell Growth Factor

Country	Effective Date	Description of action taken Grounds for decision
Singapore		The National Pharmaceutical Administration in the Ministry of Health has restricted the use of aldesleukin to medical oncologists in view of life-threatening toxicities, which have been reported with the drug. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Amineptine**

CAS number: **57574-09-1**

Synonyms: 7-[(10,11-Dihydro-5H-dibenzo{a,d}cyclohepten-5-yl)amino]hepatanoic acid hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Brunei Darussalam	June 1999	The Medical Health Services Headquarters in the Ministry of Health has withdrawn all tablets of amineptine (Survector) from the market with effect from 30 June 1999. (Reference: Official letter to Regulatory Agencies, Servier Singapore, February 1999.)
France	January 1999	The Medicines Agency has announced that the marketing authorization for the antidepressant, amineptine (SurvectorR: Servier) has been suspended and withdrawn in France. These actions have been taken after an evaluation of amineptine revealed a potential for abuse and risk of dependence. (Reference: Infofax Pharmacovigilance, Agence du Médicament, Saint-Denis, 22 January 1999.)
Italy	1999	
Morocco	June 1999	The National Advisory Commission for Pharmacovigilance has decided to suspend the marketing authorization for amineptine. This action is based on international data concerning the potential abuse and risk of dependence associated with the intake of this product. (Reference: Letter from the Directorate of Medicines and Pharmacy, Rabat, 24 August 1999.)
Oman	April 2000	The Directorate General of Pharmaceutical Affairs & Drug Control has rescheduled amineptine as a non-psychotropic restricted controlled item because of international data concerning its potential abuse and risk of dependence. (Reference Circular No. 25/2000 Directorate General of Pharmaceutical Affairs, Ministry of Health, Sultanate of Oman 25/4/2000.)
Thailand	January 1999	The Ministry of Health has withdrawn preparations of amineptine following action taken in France. (Reference: E-mail communication from the Food and Drug Administration, Ministry of Health, Bangkok, Thailand, 28 January 1999).
United Arab Emirates	12 January 1999	The Ministry of Health has banned the sale of amineptine on account of a potential for abuse and risk of dependence. (Reference: Communication with WHO, 10 July 2000.)
Viet Nam	August 1999	The Drug Administration of Viet Nam in the Ministry of Health has withdrawn approval for the antidepressant, amineptine (Survector). This follows the decision taken by France to suspend amineptine on the basis of abuse and dependency potential. (Reference: Directive from Ministry of Health, Drug Administration of Viet Nam, No. 41/1999/QD-QLD, 5 August 1999.)

Product name: **Amfepramone hydrochloride**

CAS number: **134-80-5**

Synonyms: Dethylpropion hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	April 2000	The Medicines Control Agency has banned the anorectic agent, amfepramone hydrochloride on the basis of a European Commission decision stating that risks outweigh the benefits. (Reference: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Aristolochia**

CAS number:

Synonyms:

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	July 1999	The Medicines Control Agency has banned the import, sale and supply of medicinal products containing the Chinese herbal medicine Aristolochia. This was on account of end-stage renal failure associated with the use of this product. (Reference: Statutory Instrument no. 2889 The Medicines (Aristolochia) (Temporary Prohibition) Order 1999 which came into force 28 October 1999.)

Product name: **Astemizole**

CAS number: **68844-77-9**

Synonyms: 1[(4-fluorophenyl)methyl]-N-[1-[2-(4-methoxyphenyl)ethyl]- 4-piperidinyl]-1H-benzimidazol-2-amine

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	Astemizole has been voluntarily withdrawn on the basis of prolongation of the QT-interval and ventricular arrhythmias. (Reference: Communication to WHO, 9 August 2000)
Brunei Darussalam	July 1999	The manufacturer withdrew astemizole worldwide because of serious adverse cardiovascular reactions. (Reference: Official letter to Regulatory Agencies, Jansses-Cilag, 1 July 1999.)

Mauritius	June 1999	Astemizole was withdrawn from the market following reports of adverse drug reactions published by the FDA and the decision of Janssen Pharmaceutica to remove the drug in the USA. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)
Philippines	1998	The Department of Health Bureau of Food and Drugs have noted the voluntary withdrawal by the sponsoring company of the antihistamine, astemizole due to its association with severe cardiac adverse events when used inappropriately with contraindicated drugs. (Reference: Communication from the Department of Health and Bureau of Food and Drugs to WHO, 15 August 2000.)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has banned astemizole since it has been associated with adverse drug reactions including irregular heart rhythms and severe allergic reactions if taken at higher than recommended doses or in conjunction with some other drugs including antihypertensives and anti-asthmatics. (Reference: Communication to WHO, 2 August 2000.)
South Africa	1999	The South African Medicines Control Council has withdrawn products containing astemizole because of the potential for serious drug interactions. (Reference: Information from the Pharmaceutical Services in the Ministry of Health in South Africa.)
Tanzania	2 July 1999	The Pharmacy Board of the Ministry of Health, in the United Republic of Tanzania has withdrawn astemizole from the market. (Reference: Communication to WHO from the Ministry of Health, Tanzania, 20 November 2000.)
United Kingdom	1998	Astemizole has been reclassified to Prescription only Medicine as a result of new data on interactions from postmarketing surveillance studies. These data highlight an increased risk of QT prolongation with concomitant administration of oral or parenteral formulations of azole antifungals, macrolide antibiotics except azithromycin, selective serotonin reuptake inhibitors, HIV protease inhibitors and mibefradil (now withdrawn worldwide). In addition, astemizole is contraindicated for use in patients with hepatic dysfunction. (Reference: The Pharmaceutical Journal 261, p.9, 4 July 1998.)
United Arab Emirates	June 1999	The Ministry of Health has banned the sale of astemizole with effect from 23 June 1999 on account of increased risk of QT prolongation with concomitant administration of oral or parenteral formulations of azole antifungals, macrolide antibiotics except azithromycin, selective serotonin reuptake inhibitors and HIV protease inhibitors. (Reference: Communication with WHO, 10 July 2000
USA	1999	Janssen, the manufacturer of the histamine H1-receptor antagonist, astemizole, (HismanalR) has announced that it is voluntarily withdrawing the 10-mg formulation from the market. Since the drug's approval in 1988, new adverse reaction data has necessitated a series of labelling changes and warnings. In the light of the choices of other prescription antihistamines now available and the overall risk benefit profile of this drug,

		the Food and Drug Administration supports the decision of the company to withdraw the product. (Reference: FDA Talk Paper T99-29, 21 June 1999.)

Product name: **Bromfenac**

CAS number: **91714-94-2**

Synonyms: AHR-10282; Sodium[2-amino-3-(p-bromobenzoyl)phelyl]acetate sesquihydrate

Country	Effective Date	Description of action taken Grounds for decision
Saudi Arabia	June 1999	The Ministry of Health has withdrawn from the market products containing bromfenac because of reports of liver failure, sometimes fatal. (Reference: Communication from the WHO Regional Office for the Eastern Mediterranean enclosing a notification from the Ministry of Health, Saudi Arabia, 20 June 1999.)
USA	June 1998	Wyeth Ayerst Laboratories have voluntarily withdrawn from the market capsules of bromfenac sodium, a nonsteroidal anti-inflammatory analgesic indicated for the short-term management of acute pain. This action was taken on the basis of reports of severe hepatic failure resulting in four deaths and 8 liver transplants. (Reference: Federal Register 64 (44): 10944-10947, 1999.)

Product name: **Buprenorphine**

CAS number: **52485-79-7**

Synonyms: 21-cyclopropyl-7-alpha-(S)-1-hydroxy-1,2,2-trimethylpropyl)-6,14-endo-ethano-6,7,8,14-tetrahydro-oripavine

Country	Effective Date	Description of action taken Grounds for decision
Mauritius	2000	The Ministry of Health and Quality of Life has listed buprenorphine as a Schedule II medicine under the new Dangerous Drugs Act 2000. This is because abuse of the drug by intravenous as opposed to oral use has been reported to cause a number of deaths. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)

Buprenorphine: "Field Trials" of a New Drug

Michael Agar
Philippe Bourgois
John French
Owen Murdoch

Buprenorphine is being introduced as a new treatment drug for narcotics addiction in the United States. The authors were asked by the National Institute on Drug Abuse to conduct a field trial to determine if buprenorphine might play a role in street markets. Because no street use of the drug existed in the United States, the authors used three sources of information: (a) "street readings" of clinical studies, (b) Internet discussion lists, and (c) research in other countries. By using an emergent style of analysis that relies on replication of patterns across disparate data sources, it was determined that buprenorphine has desirable characteristics from a street addict point of view. An evaluation of the field trial 5 years later evaluates its accuracy.

Buprenorphine is a new treatment drug for heroin addicts in the United States. Like methadone, it is an opioid *agonist*; that is, it satisfies the craving for a narcotic and prevents the withdrawal syndrome. Unlike methadone, it is also an *antagonist*; that is, it reacts against opiates and precipitates withdrawal. According to Navaratnam (1995), the agonist effect operates up to a certain dosage level, at which point the antagonist effect begins to operate.

We were asked by the National Institute on Drug Abuse to find out if buprenorphine currently played any role in U.S. street drug markets. From the medical and legal points of view, the question was one of what these fields call the "abuse liability" of a proposed treatment drug. Would the new treatment medication also turn into a hot street commodity, as it happened with methadone in the 1970s? Few programs used buprenorphine at the time of the study in 1996, so it played no street role in the United States, at least not among numerous different networks in San Francisco, Baltimore, and Newark. Because few users existed in the United States, we decided to experiment with the idea of a "field trial" for the drug, as opposed to the traditional notion of a "clinical trial." The "field" concept was borrowed from

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cultural anthropology with its emphasis on fieldwork, although field here is used differently from that traditional term. The logic of the field trial runs like this:

1. The field is expanded from a focus on a particular human group to *any* information available on the topic of interest, whether in the United States or in other countries, whether presented in media or a conversation, whether scholarly or popular in nature.
2. The field contains examples of use that vary in set and setting. The researcher's problem is to locate and organize set/setting information that is already available along the lines of the concept of the "natural experiment."
3. Analysis features emergent search for pattern, a style that is traditional in anthropology but also found in such areas as complexity theory (Waldorf, 1992) and marketing research (Michman, 1994). Validity derives from replication of patterns across disparate sources.
4. The analysis is anchored in a particular perspective from which the patterns are evaluated. In this case, the perspective will be that of urban American street addicts, a population with which we have decades of collective experience.

Our goal, then, is to present a field trial designed to forecast whether buprenorphine might play a role as a street narcotic in the United States and to estimate the chances that this situation might come about. To accomplish this goal, we will review a variety of different field sources and look for emergent patterns that replicate across this material from a street addict point of view. Our model of that point of view is derived from prior ethnographic work.

BUPRENORPHINE

Buprenorphine does have a history in the United States as a medication with a corresponding literature that evaluates it. This professional literature will be examined with a different filter snapped over the lens to give it a "street reading." How would this literature make buprenorphine sound if one were an opiate addict looking to buy it in a street market? Even in the technical literature, buprenorphine clearly has some desirable characteristics from this point of view. From various online literature abstracts, we learn that buprenorphine compares favorably with morphine in the management of postoperative pain. In fact, the literature suggests longer lasting and more moderate effects.

A clinical study of 6 men with histories of opioid use also adds credibility to the hypothesis (Pickworth, Johnson, Holicky, & Cone, 1993). Those who received intravenous buprenorphine rather than a placebo reported increased positive responses to a "feel drug" question and higher scores on scales of liking, good effects, euphoria, and apathetic sedation. The authors concluded that buprenorphine has substantial abuse liability when administered intravenously.

Another study, meant to test comparative effects of sublingual versus subcutaneous use, reported varying degrees of euphoria and little dysphoria and sedation from buprenorphine, also noting that "subject liking" was reported by both subjects and observers (Jasinski, Fudala, & Johnson, 1989). And finally, in what must be one of the first clinical studies of the drug (Jasinski, Pevnick, & Griffith, 1978), buprenorphine is described as having potential as a treatment drug because it is acceptable to addicts, has prolonged action, and produces a low level of physical dependence

such that addicts may easily detoxify. Such reasons are, of course, also the reasons why buprenorphine would be of interest from a street point of view as well.

Buprenorphine appears, hypothetically, as a longer, gentler "high" when compared to morphine. Returning to the abstracts, we learn that buprenorphine also has some history as an experimental drug for the treatment of opioid addiction in the United States. The effects of buprenorphine were evaluated using a rapid dose-induction procedure among 19 heroin-dependent men (Johnson, Cone, Henningfield, & Fudala, 1989). During the first 4 days of transition from heroin to buprenorphine, patients reported significantly elevated ratings of good effects, feelings of overall well-being, and decreased ratings of overall sickness. Euphoria increased and dysphoria and sedation decreased after buprenorphine administration.

A second study by the same team added that buprenorphine offered greater control of opioid withdrawal symptoms and that between-dose intervals of 48 hours could be tolerated (Fudala, Jaffe, Dax, & Johnson, 1990). In a later study (Johnson, Jaffe, & Fudala, 1992), 8 mg of buprenorphine per day compared favorably with 60 mg of methadone in treating illicit opioid use and maintaining patients in treatment. Yet another study showed that buprenorphine doses of 2 mg/day compared favorably with 30 mg/day of methadone in a heroin detoxification program (Bickel et al., 1988).

The effects of buprenorphine versus placebo on patterns of operant acquisition of heroin and money were studied in 10 male volunteers with a history of heroin addiction (Mello, Mendelson, & Kuehnle, 1982). Subjects were maintained on 8 mg/day of buprenorphine for 10 days during which they could earn money ($1.50) or heroin (7 or 13.5 mg/injection IV) by responding on a second order schedule of reinforcement for approximately 90 minutes. Buprenorphine subjects took only between 2% and 31% of the total amount of heroin available, whereas placebo subjects took between 93% and 100%.

These studies confirm that buprenorphine might serve as a desirable substitute for heroin. But would it? This is a difficult question to answer when talking about the United States because the drug is not available. In other countries, though, buprenorphine has a different history. By scanning international studies where buprenorphine is available, we might get some clues about what could happen in the United States. What follows is a brief review of some samples of international research on buprenorphine that we found in the abstracts.

Fifty known drug addicts (median age 28.6 years) admitted to a Marseille Hospital in France between June and October 1992 were examined (Arditti et al., 1992). Buprenorphine was identified in urine in 9 (18%) of them. In another study in Scotland, the effects of prescribing restrictions on the incidence of buprenorphine hydrochloride (Temgesic) are reported (Stewart, 1991). Three months after the restrictions were imposed, the rate of abuse dropped but then rose again over the next 8 months to nearly prerestriction values. Furthermore, as buprenorphine use declined, other opiate use doubled. The restrictions resulted in only a temporary drop in the availability of the drug.

In a second study from Scotland, researchers reported that 51% of opioid misusers in 1988 and 70% in 1990 were receiving prescribed opioids before assessment (Griffin, Peters, & Reid, 1993.) They report that, in the prior month, injectable opioids such as Temgesic (buprenorphine) were significantly more common in 1988 than in 1990. Although there are some indications of street use of buprenorphine in

England, the reports are less compelling. One article (Strang, 1991), for instance, describes a pattern of use in which sublingual tablets are crushed and the resulting powder inhaled. In another study, a description of 150 drug users in a London general practice indicates only 5 cases of reported buprenorphine use as opposed to 121 cases of reported heroin use (Cohen et al., 1992).

Another study from Finland (Hakkarainen & Hoikkala, 1992) reports on a policy debate over buprenorphine. During the 1980s, increasing Temgesic abuse was noted, and the drug was classified under the narcotics legislation. The status of that classification is under review. Barcelona also reported problem use of buprenorphine (San, Torrens, Castillo, Porta, & De La Torre, 1993). In studies carried out in 1988 and 1990, illicit use at some time was reported by 66% (1988) and 71% (1990) of patients in treatment, with respectively 5.9% and 6.1% actually testing positive for the drug. More than 70% of those with buprenorphine experience reported intravenous use. Australia also showed concerns about buprenorphine. One case study describes an intravenous buprenorphine addict with a history of injecting 4.5 mg/day for a period of 2 months (Quigley, Bredemeyer, & Seow, 1984). Other articles discuss general policy issues around the control of buprenorphine and its potential liabilities (Lebedevs, 1985; Wodak, 1984).

In a presentation at the 1995 College of Problems on Drug Dependence meeting, Kumar, Mandell, Shakuntala, and Daniels (1995) offered a poster session on buprenorphine use in Madras, India. Among 250 injecting drug users recruited in an HIV outreach, 96% had used buprenorphine—74% in the previous 30 days—and 44% were DSM III-defined buprenorphine dependent at the time of the interview.

Dr. Kumar was fortuitously encountered by the senior author at a conference. He described the history of buprenorphine use in detail. The upshot was that a dramatic increase in heroin availability created a population of addicts in the 1980s, but later political events and harsher laws resulted in a heroin shortage. Buprenorphine, manufactured locally in Tamilnadu State, provided an alternative for addicts, and its use rose dramatically. One unfortunate consequence of the shift was that buprenorphine—available in ampules—was injected, whereas heroin had been smoked. When heroin did return to the street market, addicts carried the new practice of injecting with them, with obvious increases in HIV risk.

Information on Bangladesh is contained in a report by Ahmed and Ara (1995). Their interviews with 30 addicts in treatment reveal the establishment of buprenorphine as a street drug, beginning in 1992, in response to declining quality and increasing cost in the heroin market. All 30 used buprenorphine daily and praised it for staving off withdrawal, pleasurable effects, and ease of use—it must be injected less frequently than heroin and its availability in ampules makes for simpler preparation.

These studies do not directly answer our question of whether buprenorphine might become a commodity with competitive value in the U.S. street market. But they do show that buprenorphine has appeared as a street drug in several other countries—France, Finland, Scotland, England, Spain, Australia, India, Bangladesh—to one degree or another. The studies support the hypothesis that buprenorphine is actively sought out and that it is something that addicts in street settings are motivated to obtain. This positive view of buprenorphine's effects held by heroin addicts suggests a potentially successful street "product." Other studies—international and U.S. based—add to the possibility of success by showing how buprenorphine interacts with other street drugs in ways similar to heroin and methadone.

In Scotland, researchers reported that 727 new needle-exchange clients (93% of the total) completed an intake questionnaire in 1992 (Gruer, Cameron, & Elliott, 1993). The most common drugs injected were heroin, buprenorphine (Temgesic), and temazepam, injected by 61%, 45%, and 28%, respectively. Most clients regularly used at least two drugs, typically heroin or buprenorphine and a benzodiazepine. Another study of a 13-week detoxification program using buprenorphine and behavioral therapy reported that 89% tested positive for benzodiazapenes and 63% for cocaine at least once during the program (Bickel, Amass, Higgins, Badger, & Esch, 1997).

From a *Scientific American* article comes a report of buprenorphine featuring both its agonist and antagonist effects (Holloway, 1991). The article notes that Jack H. Mendelson, who had recently completed a study of 12 heroin and cocaine users taking buprenorphine, suggested that high doses of buprenorphine might enhance cocaine's effects. Mendelson's concerns are supported by a clinical study from the Connecticut Mental Health Center (Rosen, Pearsall, McDougle, Price, & Kosten, 1993). In a double-blind study of 5 cocaine- and heroin-dependent patients who had been drug free for at least 36 hours, it was found that subject ratings of cocaine's pleasurable effects as well as pulse increases resulting from cocaine use were both enhanced by buprenorphine. In his dissertation on cocaine use, Erin Brown (1993) notes that the effect of cocaine was "potentiated" by coadministration of buprenorphine and that the two drugs can act together in a synergistic manner.

These studies echo two common patterns of polydrug use among heroin addicts in the United States. According to the first one, a mix of heroin and cocaine called a "speedball" is used; in the second pattern, the effects of either heroin or methadone are boosted with benzodiazapines. The sources just cited suggest that buprenorphine fits such patterns in the same way.

The literature shows that buprenorphine's effects are desirable from a street addict's point of view, it has already appeared as a street drug in several countries, and it mixes with benzodiazapines and cocaine in ways already established in street patterns of heroin and methadone use. In addition, we asked about buprenorphine on an illicit drug listserve as another source of information for this field trial.

John French logged onto a drug discussion group on the Internet and asked about buprenorphine. The three elaborate comments he received in reply echoed the themes in the literature.

1. You can think of buprenorphine as providing opiate replacement therapy similar to methadone maintenance, but with a somewhat more interesting drug. Buprenorphine is a mixed opioid agonist/antagonist, meaning that it has some effects that are like morphine and heroin, and others that block the actions of the drug. It also seems to bind to opiate receptors in the body for a very long time, so its effects are very long lasting. Basically, buprenorphine is enough like heroin that it doesn't seem to induce a withdrawal syndrome in someone who is already addicted to morphine, methadone or heroin. Buprenorphine is also "enough" like heroin that it seems to have a mild euphoric effect, at least at low doses, so there's a bit of an incentive for former addicts to use it. Buprenorphine is not very addictive on its own (though it has seen some recreational use in areas where it's freely available). It also blocks the effects of other opiates like heroin almost completely, so someone shooting up with heroin while taking buprenorphine wouldn't achieve the high they expected.
2. In places like Scotland where the heroin supply is erratic, there is a greater reliance upon various pills. Temgesic grew in popularity because for a while, the medical profession thought that they had little potential for misuse. In fact, because they were

designed to dissolve by being placed under the tongue, it was discovered that they were quite a reasonable tablet to inject as they were not laden with chalk. The strange thing about Temgesic is that they are an opiate antagonist. This means that if you've got a smack habit and you do some Temgesic, you'll end up in withdrawal. On the other hand, if you don't have a habit at all, they have an opiate-like effect. They have become popular with injectors who lack access to "real" injectable opiates in places like the Outer Hebrides.

3. There are some trials in the US at the moment I believe. I am working as a physician at a Dutch methadone programme. I started to prescribe Buprenorphine nearly a year ago in some cases: people who want to stop using opiates (it's easier to quit with buprenorphine than with methadone) and who don't want to use any other opiates (it's not working well together with other opiates). My clients (that's what patients are called) are mostly very satisfied. It is a synthetic opiate partly agonist/antagonist. It's used as a pain-killer in Holland. It must be available in the US, too.

Thus, Internet comments from those knowledgeable about buprenorphine dovetail with the reported results, suggested hypotheses, and research questions based on materials in the literature. If we summarize the different sources of information reviewed in this section, we get the following field trial results for buprenorphine:

1. Buprenorphine has characteristics that compare favorably with the desirable characteristics of morphine, methadone, and heroin. Furthermore, buprenorphine may have fewer undesirable characteristics than those drugs.
2. There are indications that buprenorphine use lends itself to polydrug use in ways similar to heroin and methadone.
3. Buprenorphine can play a role in "habit management"; that is, in situations in which a preferred narcotic is not available, buprenorphine can be used to stave off withdrawal and provide an agonist effect.
4. Buprenorphine may be the preferred narcotic in locations where heroin is not available.
5. Buprenorphine might have characteristics that lead it to become a preferred narcotic in its own right, even in a market that offers several available options.

At the end of this review, we can say that it is clear that buprenorphine has a potential role to play in the streets. We can forecast a "possible world" within which buprenorphine would find a street market in the United States. In fact, we can give an optimistic street reading on buprenorphine based on what we learned, a provisional but plausible one, given the material at hand: "Buprenorphine is a nice mellow high and it lasts a long time. It's easy to kick, it makes a good speedball, and you can boost it with benzodiazapines."

The results of this field trial are clear. Could buprenorphine possibly develop into a street drug in the United States? Yes, it could. We return to this question and the subjunctive verb *could* in the conclusion.

THE ANTAGONIST MIX

After this field trial began, we learned that a focus on buprenorphine alone would no longer answer the question about potential street use. Even as we did this study, interest in the United States was shifting from buprenorphine as a stand-alone treatment to a mix of buprenorphine and *naloxone*, a narcotic antagonist. Even though buprenorphine already has an antagonist effect, that effect—as we have seen—clearly

does not discourage street use. Naloxone, supposedly, would beef up the antagonist and make the drug less attractive in the streets. However, such a strategy would also make it less attractive with respective implications for recruitment and retention in treatment.

Dr. John Mendelson, who was cited earlier in the literature review, showed us the results of a new study in which buprenorphine was compared with a buprenorphine/naloxone mix during an interview with Agar and Bourgois. According to evaluations obtained from 10 subjects, buprenorphine alone was a desirable drug with a high street value. But the high user ratings of buprenorphine alone plunged when naloxone was added. The potential problem with the buprenorphine/naloxone mix lies in the classic problem with antagonists in the past. Their history shows that the few patients who succeed tend to be of higher socioeconomic status with a prior commitment to quit their narcotics addiction. It is no surprise that most addicts, when offered something that will make them sick and will never get them high, do not find the offer attractive.

Nonetheless, the focus in future U.S. clinical trials apparently will be on buprenorphine/naloxone mixes. In an interview with Agar, Dr. Richard Resnick pointed out that the addition of naloxone to buprenorphine is meant to prevent its diversion into the streets. The sublingual dose of naloxone will not affect the buprenorphine, but an individual who is addicted to heroin will feel the effects of withdrawal. The new mixture will also offer commercial and marketing advantages from the manufacturer's point of view.

We wonder if possible strategies could be developed in the streets to manage the antagonist component of the new buprenorphine/naloxone mix. Numerous shifts in street pharmacology over the years have been observed as users have changed drugs, modes of preparation, perception of effects, and styles of use. Both Mendelson and Resnick, in interviews with us, argue that this will not occur. However, it will be an important exercise to monitor the "street trials" that will follow the clinical trials if and when buprenorphine/naloxone becomes a widely used treatment modality.

THE STREET/TREATMENT BOUNDARY

We would like to make it clear that we came to this study neither to praise nor to bury buprenorphine. Our judgment at the end of this field trial is that buprenorphine alone appears to be a worthwhile alternative treatment modality to methadone, at least worthy of further study. However, buprenorphine alone will likely lend itself to street use, as methadone did when it was introduced in the 1970s.

Mendelson, in an interview with Agar and Bourgois, pointed out possible advantages of the shift to buprenorphine: (a) Buprenorphine does not have the negative or "loser" image that methadone has acquired over the years; (b) one cannot overdose on buprenorphine, although frankly we are still wondering about agonist/antagonist interactions in the context of the normal polydrug street environment; (c) buprenorphine is not as euphoric as methadone, although again the same thing was said of methadone when it was first introduced, and the literature reviewed earlier sometimes suggests the contrary; and (d) with its longer acting effects, buprenorphine

will be cheaper to administer, requiring a visit to a clinic site every few days instead of daily.

Resnick, who has experimented with buprenorphine as a treatment modality for some time, argues that the drug has other advantages as well (Resnick & Falk, 1987; Resnick et al., 1992; Resnick, Resnick, & Galanter, 1991). Stressing the diversity of the addict population, Resnick finds that buprenorphine may appeal to addicts who will not enter the health care system via methadone treatment or therapeutic communities and who are not motivated to use a narcotic antagonist. Such addicts show a higher level of psychosocial functioning when compared to nonresponders in his studies. Buprenorphine proves useful in detoxification as well, he adds.

But how do we reconcile an interest in buprenorphine as an alternative treatment for heroin addiction—something clearly supported by our two interviewees and three of the four authors of this article—with our field trial results that show buprenorphine's possible future as a street drug? Based on our collective experience with methadone maintenance over the years, we would argue that it is not a matter of reconciling a contradiction. Instead, it is a matter of accepting that you cannot have one without the other. An effective maintenance drug will always be interesting to the streets as well.

When methadone was first proposed as a maintenance drug in the 1960s, it initiated an experiment that had not been tried for decades. Since the closing of the U.S. morphine clinics in the 1920s, if one wanted treatment, one had to eliminate physical dependence right at the beginning. Treatment started only after detoxification. Relapse rates after such treatment were uniformly high. With methadone maintenance, things changed. Now an addict could enter treatment without first kicking the habit. In fact, by some program philosophies, one would never have to kick the habit.

In other words, methadone clouded the boundary between treatment and the streets more than ever before. Now treatment included taking an opiate, rather than requiring that opiate use cease before treatment started. Methadone accommodated an addict's world and, compared to any other drug-free treatment, made it easier for him or her to experiment with a "patient" role. Treatment evaluations showed a higher retention rate for methadone compared with drug-free modalities. But then, the other side of the story is this: If a treatment modality accommodates the street world, then the street world can incorporate the treatment modality. Historically, we saw this happen with methadone, as a "medication" from the clinical point of view also became a commodity in the street markets (Agar, 1977; Agar & Stephens, 1975; Preble & Miller, 1977).

When the boundary between street and treatment turns fluid and fuzzy as it did with methadone, the treatment drug is no longer either "medication" or "dope." It is both. Buprenorphine is another chemical move in this treatment game. With its widespread use as a treatment drug in the United States, it will probably develop a street market here as well. In the next section, in which we discuss in more detail the current buprenorphine situation in France, we will see that it has, in fact, become an exceptionally popular street drug in that country and that it is injected rather than used sublingually as originally intended.

Interesting and problematic will be the development of buprenorphine/naloxone mixes. Efforts to use naloxone to build a wall against street use may, by this logic, recruit fewer addicts and resemble the limited role that antagonists alone

have always played. The paradox, again, is this: A medication with powerful and effective outreach and recruitment into treatment is also a drug with a role to play in street markets. With apologies to Gunnar Myrdal, we might call this the "American treatment dilemma" and simply close by hoping that our field trial clarifies its inevitable and enduring presence.

A YEAR-2000 UPDATE

Roughly 5 years have passed since we conducted the research on which this article is based. Since that time, needless to say, the buprenorphine story has continued. In this brief update, we first look at some of the recent literature to check whether the field trial holds up. We searched MedLine with key words *buprenorphine*, *human*, and *abuse* and came up with about 80 abstracts since 1995. After a brief review of this literature, we will take a look at the current situation in France, where the liberalization of prescription laws for sublingual buprenorphine in 1996 increased the street market noticeably. In fact, underground economy sales are so robust that the street price of buprenorphine is actually cheaper than the pharmacy price. Finally, we will briefly look at how buprenorphine has become more of a newsworthy topic in the United States. In general, our review of this new material will show that, with a few minor exceptions, the field trial of 5 years ago was accurate.

In recent years, the professional literature has continued to grow, with many reports evaluating buprenorphine—often by comparison with methadone—and concluding that the new drug does indeed have a role to play in the treatment of heroin addiction (see, for example, O'Connor et al., 1996, 1998; Petry, Bickel, & Badger, 1999). Some studies now discuss a lower retention rate for buprenorphine when compared to methadone (Eder et al., 1998; Fischer et al., 1999). There is more recognition of the drug's abuse liability, although articles still neglect street views of buprenorphine, and street voices commenting on the drug are absent.

Earlier we argued that one signal of buprenorphine's desirability from a street point of view was its ability to mix with other drugs in ways similar to heroin and methadone. By and large, this statement is still supported (see, for example, Schottenfeld, Pakes, & Kosten, 1998). However, the recent literature is more equivocal on the mix of buprenorphine and cocaine. In one comparison of methadone and buprenorphine, it is reported that the buprenorphine treatment sample produced fewer cocaine-positive urines, although the difference was not statistically significant (Eder et al., 1998). Another study concludes that buprenorphine may be more effective than methadone for controlling cocaine abuse (Foltin & Fischman, 1996). On the other hand, a third study questions the claim that buprenorphine reduces cocaine use more than methadone does (Schottenfeld, Pakes, Oliveto, Ziedonis, & Kosten, 1997).

Clearly, the jury is still out on the mix of cocaine and buprenorphine. This contrasts with our statements that cocaine mixed well with the drug. However, the ability of buprenorphine to blend in with benzodiazapines has held up (Eder et al., 1998). A comparison of buprenorphine and methadone patients showed no difference in use of benzodiazapines or alcohol (Schottenfeld et al., 1998). In the French case discussed below, one article actually reports several deaths caused by

buprenorphine/benzodiazapine mixes (Tracqui, Kintz, & Ludes, 1998), and another suggests that the two drugs are sometimes coprescribed by physicians (Seyer, Dif, Balthazard, & Sciortino, 1998). Ethnographers and outreach workers present the mixing of buprenorphine and benzodiazepines—especially Rohypnol—as a matter of street-based common sense (Kempfer, 1998a, 1998b; A. Lovell, personal communication, May 29, 2000.).

Another part of the field trial based on the 1996 research focused on the future of buprenorphine/naloxone mixes. Several research articles report on this mix during the past 5 years, and the news is pretty much as we forecast earlier. Mendelson, whom we interviewed for the original research, reported that a buprenorphine/naloxone combination precipitated withdrawal and was unpleasant and that half the subjects could not distinguish between naloxone alone and the mix during the first hour of the experiment (Mendelson, Jones, Welm, Brown, & Batki, 1997). Another study reports that the mix produced opiate withdrawal, and it suggests explicitly that this will reduce buprenorphine's street value (Nath, 1999). These studies describe such outcomes as an advantage, a way to reduce the abuse liability of buprenorphine. In our field trial, we argued that, from a street perspective, the mix would reduce interest in buprenorphine/naloxone in the street markets, but it would also reduce interest in the mix as a treatment drug. Indications in the recent literature suggest that our argument, based on the earlier research, still holds up.

In the 1996 research, we scanned international studies of buprenorphine to see if it had become a street drug in the countries where it was more available. The studies we located suggested that it had, and this conclusion led us to strengthen our forecast for the future street role of buprenorphine in the United States. For this update, Bourgois, whose professional contacts and language abilities made a look at recent developments in France possible, contacted colleagues and looked at some literature. Fortuitously, Anne Lovell, an anthropologist with the University of Toulouse and researcher with INSERM (the French equivalent of the National Institutes of Health), contacted Agar on another matter as we were revising this article, and her detailed suggestions and advice made much of our summary possible.

The street history of buprenorphine in Europe—especially France—teaches us a great deal about the potential appeal of the drug among street addicts. It was initially developed as an injectable painkiller in the United Kingdom in 1978 under the trade name Temgesic and was soon marketed throughout most of Europe. In France, it became relatively widely available in 1987 but solely in injectable form. By 1990, its distribution was curtailed due to reports of street abuse, and the injectable form was limited to hospital pharmacies. In 1996, it became widely available through unrestricted medical prescription from general practitioners in a sublingually administered form known under the trademark Subutex intended exclusively as a substitute treatment for heroin addiction. By the year 2000, approximately 58,000 addicts were officially on Subutex maintenance compared to only 7,000 on methadone. France was the only European country where buprenorphine was so widely and systematically used in drug treatment (C. Carrandie, personal communication, May 24, 2000; Kempfer, 1998/1999; Lert et al., 1998).

According to ethnographers and outreach workers, a significant number of French maintenance patients resell their prescribed sublingual doses on the street

where they are dissolved into syringes by street addicts for injection. Unfortunately, this particular form of sublingual buprenorphine rapidly deteriorates veins and causes especially virulent abscessing when injected (Kempfer, 1998b, 2000; A. Lovell, personal communication, May 29, 2000). The lack of an ecstatic rush effect from buprenorphine exacerbates its deleterious effects on the veins of street injectors as it often provokes a cycle of compulsive repeat injection in a search for the elusive rush. As with methadone in the United States, the frustrating euphorigenic effects of buprenorphine lead to the phenomenon of low-status, multiple-substance abusers who combine alcohol and benzodiazepines with the treatment drug to try to "boost" its effects (Bourgois, 2000; Kempfer, 2000).

Perhaps the exceptional frequency with which street-based addicts inject sublingual buprenorphine in France can be explained by street market fluxes in heroin availability. In the late 1990s, street injectors in the Goutte d'Or neighborhood of Paris told Bourgois that they were forced to inject Subutex because of the poor quality of heroin in street markets. Indeed, the artificially low price of Subutex on Paris streets, approximately 10 francs for an 8 mg dose compared to 100 to 200 francs for the standard street dose of heroin, may explain the frequency with which street-based heroin addicts were injecting (Kempfer, 2000). A French outreach worker reports that buprenorphine is sold at below pharmacy cost on the street because dealers access the drug for free as indigent patients by presenting themselves for treatment to a half-dozen doctors simultaneously (Kempfer, 2000). An ethnographer based in Marseilles confirms that Subutex is an inexpensive alternative to heroin for street addicts and that it is sometimes called a poor man's heroin (A. Lovell, personal communication, May 29, 2000.). Nevertheless, it is widely used on the streets of both cities. In a study of street-recruited heroin injectors in Marseilles, 23% were current Subutex injectors (Lovell, in press). Treatment centers in Paris similarly report detoxing addicts who are exclusively injectors of Subutex (C. Carrandie, personal communication, May 24, 2000). Outreach workers and ethnographers also report that some younger addicts have exclusively had careers of Subutex injection (see also Kempfer, 2000), and even nonaddicts will use Subutex as an occasional party drug (A. Lovell, personal communication, May 29, 2000.). Of course, a silent majority of French addicts do use buprenorphine to "normalize" and mainstream their lifestyles, as it was intended (Lovell, in press).

The French scenario of a relatively high street demand for buprenorphine among injectors may be somewhat specific to the culture of French substance abuse, which revolves especially intensively around needle use. This is suggested, for example, by the fact that a disproportionately high number of crack users in the Goutte d'Or neighborhood that Bourgois visited in the late 1990s insisted on injecting crack instead of smoking it (Kempfer, 1998b; Lefort, 1998). The easy accessibility of buprenorphine by general practitioner prescription in France also contrasts dramatically with the extremely limited access of addicts to methadone maintenance. And finally, buprenorphine in France does *not* have the antagonist mixed in, as the United States now plans to do. If it did, injection of the sublingual dose would precipitate withdrawal.

The French case shows—with more depth than the earlier review of the international literature allowed—how treatment policy, market conditions, and cultural

dynamics might combine to enable a flourishing buprenorphine street scene to develop. Another interesting change since the earlier research is the degree to which buprenorphine has become more of a public topic in the United States, although we anticipated this from the reaction with which an earlier draft of this article was greeted by the original sponsors, who saw undesired qualifications around the development of a promising new treatment drug. However, the senior author was contacted in early 2000 by the Center for Substance Abuse Treatment of the U.S. Public Health Service. They had obtained an earlier version of this article and asked if they might use it in their role to regulate buprenorphine-based treatment. We sent them the manuscript and asked for information that we might use as part of the revision in this update section. Unfortunately, they did not respond.

Buprenorphine has also become "news" for the general public, if a recent article in *USA Today* is any indication (Leinwand, 2000). A front-page feature is titled "Heroin's New Fix and Why It Matters to You." The feature is rather elaborate, but part of it discusses buprenorphine, which is one example of a new treatment that is "far more difficult to abuse than methadone because they are much less addictive" (Leinwand, 2000, p. 1). According to the article, a drug called Suboxone is near FDA approval—it is a mix of buprenorphine and naloxone. They note that another pill, this one only containing buprenorphine, has already been given to addicts in France. A physician and drug expert is quoted as saying buprenorphine has been a "huge success. People can function totally normally and be very alert if it's properly dosed" (Leinwand, 2000, p. 2). Along with the report on the new treatment drugs, buprenorphine key among them, the article talks about how doctors will be able to prescribe it out of their office so that clinics will not have to be set up in neighborhoods. Congress and the Drug Enforcement Agency, says the article, are in support of the change in treatment drug and prescription practice. However, there are some concerns in law enforcement that the take-home medication will appear in street markets.

We leave it to the reader, based on the material in this article, to sort through the *USA Today* feature. It seems striking that the use of buprenorphine for heroin addict treatment now warrants a feature in a widely read national newspaper. Five years ago, few people had even heard of the drug, including us when we were first contacted about this project, and many of our colleagues in the drug field. Clearly, buprenorphine will now be tried in the United States, so the acid test for our field trial and this update are now at hand. We see no reason to change our forecast. If buprenorphine alone is used, a street market will develop. If heavy doses of antagonist are mixed with buprenorphine, the mix will enjoy less success in enrolling or holding people in treatment.

At the same time, we feel that maintenance of physically dependent persons is a valuable and humane harm-reduction strategy. The fact that an attractive maintenance drug has some street value has to be accepted as part of the deal. Given that framework, buprenorphine with or without the naloxone mix, as many researchers we reviewed and interviewed for this article have said, offers an interesting new alternative to methadone that deserves a chance. It is good to remember our French colleague, cited earlier, who said that a "silent majority" of addicts used buprenorphine to buy some time to change their lives. However, buprenorphine—like methadone before it—is no "magic bullet." Unrealistic expectations for success that neglect

the realities and needs of the streets only yield surprises that could have been anticipated.

CONCLUSIONS

Does buprenorphine possibly have a future in the U.S. street markets? Possibly, without a doubt; probably, it depends.

It depends, first of all, on the results of the street trials that will inevitably follow the clinical trials, whereby *street trials* we mean actual experiments with the drug conducted by users themselves. Navaratnam (1995), cited earlier in this article, outlined a picture of buprenorphine's rising and falling effects in an interview. Over much of the curve, cocaine or benzodiazipines might be used to boost the effects without triggering the antagonist. As the curve falls, an addict could use heroin or methadone without fear of pushing the curve into the zone where the antagonist effect begins. His scenario outlined a hypothetical street trial outcome.

It also depends on the way buprenorphine is introduced. The addition of naloxone to the treatment drug increases the antagonist effect. It remains to be seen how this would effect treatment efficacy and street interest. Our prediction is that the mix will be of less interest in the streets, and it will not draw people into treatment as effectively, except for the highly motivated or those fleeing the stigma and/or inaccessibility of methadone. We could be wrong. Buprenorphine might offer enough to satisfy an addict's craving, whereas the stronger antagonist might deter use of illicit street narcotics. And we might be twice wrong if street trials develop polydrug strategies to enhance the agonist and reduce the antagonist effect, even with the added naloxone, although the experts we interviewed argue that this will not be the case.

And it depends, finally, on market conditions. Methadone was introduced at the time of the Nixon-era crackdown on the Turkey-Lebanon-France-U.S. pipeline that had delivered heroin to the United States for years. Sharp reductions in quantity and quality of heroin together with rapid increases in methadone availability led to a shift that placed methadone in a key role in the street markets. Buprenorphine's fate will also depend on market conditions, as the example of France showed so well.

Our summary reflects a forecasting effort that departs from traditional clinical trials in several ways. We consulted disparate data from the field and developed scenarios based on conditions that make outcomes more or less probable. Forecasting is different from traditional science, as recent work shows all too well (Sherden, 1998). At the same time, the forecast is useful in outlining alternative scenarios—we now know something about what might happen and the conditions that are likely to make a difference. We move into the future with an outline map rather than no map at all. Field trials, drawing on multidisciplinary and multimethodology sources from epidemiology to ethnography and from treatment research and medical anthropology to the field of jurisprudence research, clearly offer an alternative and important understanding of drugs and their future that other approaches do not provide. And with the opportunity to evaluate the mid-1990s field trial 5 years later, we can say that, in this case, the field trial worked relatively well.

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Michael Agar has worked in the drug field since 1968, most recently on the contextual explanation of drug use trends. He also consults and teaches ethnographic/qualitative methods, as reflected in his book The Professional Stranger, *and works on issues of language-based ethnography, introduced in his book* Language Shock.

Philippe Bourgois, Ph.D., is with the Department of Anthropology, History and Social Medicine in the University of San Francisco's School of Medicine. He is a cultural anthropologist who studies the interface of violence, poverty, and substance abuse with a special emphasis on the experience of ethnic discrimination among inner-city residents and among Latin American immigrants. He is currently conducting fieldwork in the homeless encampments of a network of heroin injectors in San Francisco. His most recent book, In Search of Respect: Selling Crack in El Barrio *(1995, Cambridge), won the Margaret Mead and the C. Wright Mills Prizes. He has published numerous articles on substance abuse in venues ranging from* New York Times Magazine *to* Social Problems *and* Culture, Medicine and Psychiatry.

John French is now semiretired after 30 years with the New Jersey Department of Health, where his longest and latest tenure was as the director of research for addiction services. His areas of expertise include both quantitative and qualitative methodology, as well as program administration.

Owen Murdoch received a master's degree in anthropology from the University of Maryland. In addition to conducting ethnographic research on trends in drug abuse, he has worked on designing and implementing HIV-prevention projects in Baltimore, Maryland, and Denver, Colorado. He is currently pursuing a career in medicine.

REPORT OF THE INTERNATIONAL NARCOTICS CONTROL BOARD FOR 2001

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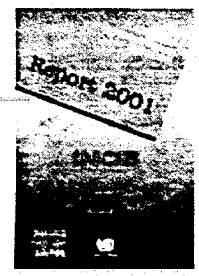

Contents

EXPLANATORY NOTES

The following abbreviations have been used in this report:

ADD	attention deficit disorder
AIDS	acquired immunodeficiency syndrome
ANMAT	National Administration for Medicaments, Food and Medical Technology (Argentina)
CICAD	Inter-American Drug Abuse Control Commission

	Commonwealth of Independent States
CONACUID	Comisión Nacional contra el Uso Ilícito de las Drogas (Venezuela)
DAWN	Drug Abuse Warning Network (United States of America)
ECOWAS	Economic Community of West African States
Europol	European Police Office
GAFISUD	Financial Action Task Force on Money Laundering in South America
GBL	gamma-butyrolactone
GCC	Cooperation Council for the Arab States of the Gulf
GHB	gamma-hydroxybutyrate
HIV	human immunodeficiency virus
Interpol	International Criminal Police Organization
LSD	lysergic acid diethylamide
MDA	methylenedioxyamphetamine
MDMA	methylenedioxymethamphetamine
MERCOSUR	Common Market of the Southern Cone
OAS	Organization of American States
OAU	Organization of African Unity
PMA	paramethoxyamphetamine
PROMIS	Police Realtime Online Management Information System (Australia)
SAARC	South Asian Association for Regional Cooperation
SEDRONAR	Secretariat for Planning the Prevention of Drug Abuse and the Fight against Drug Traf
SIDUC	Inter-American System of Uniform Drug-Use Data
THC	tetrahydrocannabinol
UNDCP	United Nations International Drug Control Programme
WHO	World Health Organization

Data reported later than 1 November 2001 could not be taken into consideration in preparing this report.

Foreword

Just as the introduction of electricity and the telephone changed lives in the twentieth century, the Internet is revolutionizing the way people live today. As with many innovations, however, the advantages go hand in hand with new problems; for the Internet, there is a real danger that its benefits might be seriously undermined by criminals for illicit gain. It is the responsibility of the International Narcotics Control Board to alert Governments and the public to any developments relating to drug abuse and trafficking. In chapter I of its report for 2001, the Board examines the challenges that new technologies, such as the Internet, pose to drug law enforcement in an era of increasing globalization.

Cyber crime—crime committed in an electronic environment—is easy to commit. It requires few resources and can be committed in one country by a person sitting safely in another. It is difficult to fight both the criminals and their crimes in this "virtual" environment, where national boundaries are irrelevant and personal risk to the criminals and the likelihood of detection are greatly reduced. Enhanced vigilance at the local level and international cooperation in the investigation and prosecution of cyber crime are essential to preventing the Internet from turning into a worldwide web of drug trafficking and crime.

In chapter II of its report for 2001, the Board reviews the operation of the international drug control system, including legislative developments in certain European countries concerning the prosecution of cannabis-related offences. The Board's opinion is that such measures will not contribute to achieving the target of significantly reducing the demand for illicit drugs by 2008, to which Governments committed themselves in the Political Declaration adopted in 1998 by the General Assembly at its twentieth special session, devoted to countering the world drug problem together. The Board has not received credible information indicating that relaxing drug laws reduces drug abuse. To the contrary, the progressive liberalizaton of drug laws in some countries over the last 20 years has been associated with a progressive increase in drug abuse.

Chapter III presents an analysis of the world situation with regard to illicit drugs. It reports on a continued reduction in cultivation of some illicit drug crops, and also on the increasing manufacture and trading of illicit synthetic drugs. It is evident from this chapter that there is nearly universal support for the three main international drug control treaties and that more than 170 States are accepting and fulfilling the obligations that being parties to those treaties entails. The parties to those treaties could not be more diverse; they include both developed and developing countries from all parts of the world, the common thread being that they have all been affected by the world drug problem in some way—illicit drug manufacture or trafficking, rampant drug abuse or exploitation of their territory for money-laundering.

The International Narcotics Control Board, whose mandate and mission originate in the international drug control treaties, wishes to emphasize that the reason for adopting those treaties was to contain the abuse of drugs. The Board notes that all those treaties emphasize the principle that the use of drugs should be restricted to medical and scientific purposes. It follows that, in this context, the term "use" or "consumption" should only be applied when it refers to the use or consumption of drugs for medical or scientific purposes. When neither of those conditions applies, in line with the international drug control treaties, the drug may be considered abused. Drug abusers are therefore, by definition, neither consumers nor users, and drugs and other mind-altering substances are not consumer goods. It is important that any attempt to minimize, trivialize or even ignore the seriousness of drug abuse by calling it drug use or drug consumption should be strongly resisted. It is also important that any careless use of terms should not lead to any contradicting or undermining of what is expressed in the treaties.

The international drug control treaties support the advancement of science and the reduction of human suffering. They explicitly stress that drugs should be available for medical purposes to relieve pain and that scientific enquiry into the use of drugs for the relief of suffering is essential. At the same time, the treaties seek to protect individuals, families and societies so that they do not become the casualties of drug dependence and addiction. For those individuals who do become such casualties, the treaties offer a humane response, with provision for treatment, rehabilitation and social reintegration. They do not, however, sanction the recreational use of drugs. It is important that the humane treatment and rehabilitation of those who abuse drugs and are dependent upon them are not confused with and do not lead to the "normalization" of drug abuse (i.e. drug abuse being accepted or considered normal). The social and recreational use of drugs constitutes their misuse and should not be "normalized", as some now advocate. Doing so might offer short-term gains in terms of saving resources but it would have profound consequences for young people today and for future generations.

The progressive acceptance of drug abuse over the past three decades, such that illegal drug use is now perceived as inevitable, will be hard to reverse. Increasingly, it is argued that drug use is a personal issue, an individual's civil right. While rights are important and must be protected, they are also inextricably linked to responsibilities, in this case societal responsibilities. Pursuit of pleasure and freedom of choice are rightly valued highly in a free society, but in relation to drugs they can also be dangerous, not just for individuals but also for society as a whole and especially for the vulnerable segments of society. The "normalization" of drug abuse is a high-risk approach to a complex problem, the prevention of which should be firmly based in scientific research.

Hamid Ghodse
President of the International Narcotics Control Board

Commission on Narcotic Drugs to all States parties and non-parties to the 1988 Convention. In accordance with the provisions of article 12, paragraph 6, of the 1988 Convention, the decision to transfer those substances to Table I becomes fully effective with respect to each party 180 days after the date of that communication, that is, on 8 December 2001. The Board wishes to remind all Governments that the provisions of pre-export notifications for both acetic anhydride and potassium permanganate, as provided for under article 12, paragraph 10 (a), is now a treaty obligation, when such notification has been requested by the importing country.

F. Ensuring the availability of drugs for medical purposes

Demand for and supply of opiates

181. The Board, while analysing annual production of opiate raw materials and consumption of opiates worldwide, examines on a regular basis issues affecting the supply of and demand for opiates used for medical and scientific purposes and endeavours to maintain a lasting balance between the two. A more detailed analysis of the supply of and demand for opiates for medical and scientific needs is contained in the 2001 report of the Board on narcotic drugs.[53]

Cultivation of the thebaine-rich variety of opium poppy on the rise

182. The Board notes that since 1998, when commercial cultivation of the thebaine-rich variety of opium poppy began in Australia, the total area under such cultivation has been on the rise. In 2000, thebaine-rich poppy straw was harvested from a total area of 5,479 hectares, compared with 809 hectares in 1998 and 1,978 hectares in 1999. If, as projected, further increases take place in 2001 and 2002, the cultivation of the thebaine-rich variety and the morphine-rich variety of opium poppy will almost be in equal proportions—around 10,000 hectares each.

Stocks of opiate raw materials increasing

183. The Board notes that overall utilization of opiate raw materials for the extraction of alkaloids has continued to follow the trend towards a larger proportion of the alkaloids being extracted from concentrate of poppy straw than from opium. That has been mainly the result of the increasing use of thebaine-rich poppy straw to respond to the growing demand for oxycodone for the treatment of pain and for buprenorphine, increasingly used in heroin substitution treatment. So far, however, the Board has not included any quantities related to thebaine in its analysis of the supply of and demand for opiates worldwide. But even without including thebaine-rich concentrate of poppy straw, in 2000, a record amount of 246.2 tons of concentrate of poppy straw in morphine equivalent were used for the extraction of alkaloids, whereas the amount of opium used dropped to 76.5 tons, its lowest level in 20 years.

184. Global stocks of opium increased further at the end of 2000, reaching 170.4 tons in morphine equivalent. A further increase was also noticed in respect of concentrate of poppy straw, stocks of which stood at 80.3 tons in morphine equivalent in 2000, having gradually increased from 35.9 tons since 1995. In general, increased production of opiate raw materials over the past few years has contributed to a substantial increase in global stocks, particularly of opium.

185. The Board notes that the Government of India has reduced considerably its projected area for opium poppy cultivation for 2002, bearing in mind its current level of opium stocks and the actual quantities of opium required worldwide for the extraction of alkaloids. The Board considers that adjustment to be a timely and positive development. The Board hopes that the Governments of producing countries will, based on their actual stocks and export requirements, make the necessary adjustments while planning their future production to ensure the continued availability of opiate raw materials and, at the same time, to prevent any imbalance caused by excessive production.

186. Considering the current levels of stocks of opiate raw materials, the Board calls the attention of all Governments to Economic and Social Council resolution 2001/17 and requests Governments to refrain from exporting and importing seized opiates or products derived from seized opiates.

Expert working group on the supply of and demand for opiates for medical and scientific needs

187. In 2001, the Board examined the work of an expert working group, composed of representatives from the main countries producing or importing opiate raw materials, to review, in particular, the methodologies used for the analysis of the global supply of and demand for opiates for medical and scientific needs. The Board endorsed the conclusions and recommendations of the expert working group.

188. In order to ensure the smooth and effective implementation of the recommendations, the Board decided, inter alia, that the Governments concerned should be requested to provide additional data related to opiate raw materials. The Board believes that the new methodologies recommended by the expert working group will provide a more accurate analysis and therefore a clearer picture of the situation and trends with regard to the supply of and demand for opiates for medical and scientific needs worldwide.

189. The Board has requested WHO to consider whether it would be more appropriate to place buprenorphine under the control of the 1961 Convention instead of the 1971 Convention, particularly in view of its increasing use in pain management and heroin substitution treatment and, therefore, its importance in the assessment of the supply of and demand for opioids for medical and scientific needs. The Board hopes that the recommendation to reschedule buprenorphine will be further reviewed by the WHO Expert Committee on Drug Dependence and eventually considered by the Commission on Narcotic Drugs.

Recommendations of the Board on the methodologies for the supply of and demand for opiates for medical and scientific purposes

190. Having considered recent developments and trends related to the use of thebaine for the manufacture of opiates and the increasing consumption of oxycodone and hydrocodone, the Board recommends, inter alia, that:

(a) Additional opiates (thebaine, oxycodone and hydrocodone etc.) be included in calculations of supply and demand;

(b) Four figures—the gross weight of the material and the estimated weight of morphine (anhydrous morphine alkaloids), codeine (anhydrous codeine alkaloids) and thebaine (anhydrous thebaine alkaloids)—be reported with respect to opiate raw materials;

(c) Utilization data be added and used for the calculation of demand for opiate raw materials;

(d) Conversion coefficients be based on the relative molecular weights with respect to alkaloids and on actual conversion rates in industrial processes with respect to opiates;

(e) Various forms be modified to incorporate additional data to be provided by Governments;

(f) Buprenorphine and oripavine be considered by WHO for possible scheduling as controlled drugs under the 1961 Convention.

Informal consultation on supply of and demand for opiates for medical and scientific needs

191. Pursuant to Economic and Social Council resolution 2000/18, on demand for and supply of opiates for medical and scientific needs, an informal consultation was organized at the request of the Governments of India and Turkey during the forty-fourth session of the Commission on Narcotic Drugs, in March 2001. The consultation, to which the Board invited the authorities of all the main countries producing and importing opiate raw materials, provided an appropriate opportunity for participating Governments and the Board to be apprised of developments in the supply of and demand for opiates in those countries.

Consumption of narcotic drugs

Consumption of drugs for the treatment of moderate to severe pain

192. There continue to be very significant differences between countries in the consumption levels of narcotic drugs for the treatment of moderate to severe pain. Although global consumption has been increasing sharply during the last two decades, the growth has mainly been attributed to several developed countries, while the use of those drugs in many other countries, in particular developing countries, has remained extremely low. Fentanyl, morphine and pethidine are

the analgesics most commonly used worldwide for the treatment of moderate to severe pain. Other opioids such as ketobemidone, oxycodone and tilidine are used for that purpose mainly in some developed countries.

193. Global consumption of morphine has increased 10 times during the last two decades. Since the beginning of the 1990s, the use of fentanyl (in particular in the form of transdermal patches) for the treatment of chronic pain has also been sharply growing. The use of oxycodone has been rising since the middle of the 1990s, particularly in relation with the introduction in the United States of slow-release tablets containing that drug (see paragraphs 120-122 above). Global consumption of pethidine is slightly decreasing.

194. In 2000, the 20 countries with the highest levels of consumption of narcotic drugs for the treatment of moderate to severe pain were Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Iceland, Ireland, Israel, Luxembourg, Sweden, Switzerland, the Netherlands, New Zealand, Norway, Portugal, the United Kingdom and the United States—all of them developed countries. The United States alone accounted for more than 40 per cent of global consumption of morphine, 55 per cent of global consumption of fentanyl and more than 90 per cent of global consumption of oxycodone. In the above-mentioned countries, as well as in several others, the consumption of narcotic drugs has been increasing as a result of constant efforts to improve pain management.

195. Governments should be aware that increasing availability of narcotic drugs for legitimate medical purposes might facilitate the diversion and abuse of those drugs. The Board invites the Governments concerned to closely monitor trends in the consumption of pharmaceutical products containing narcotic drugs and to adopt measures against their diversion and abuse.

Efforts to improve the availability of narcotic drugs for the relief of pain

196. As emphasized by the Board on several occasions,[54] it is the obligation of all Governments to ensure the availability of narcotic drugs for the relief of pain and suffering, while preventing their diversion for illicit use. Among the most frequent reasons for the unavailability of opioids are: absence of a special policy on the management of acute and chronic pain, including cancer pain; serious deficiencies in the system for assessing the requirements for narcotic drugs; budgetary constraints; overly restrictive regulations and complicated administrative procedures; concerns about the legal consequences of unintentional errors; concerns about unintended addiction; and inadequate or insufficient training of health professionals.

197. The Board welcomes the document entitled "Achieving balance in national opioids control policy: guidelines for assessment", issued by WHO in 2000,[55] in which Governments are encouraged to achieve better pain management by identifying and overcoming regulatory barriers to the availability of opioids. In the opinion of the Board, the guidelines for the review of national policies contained in that document should always be applied with full respect for the provisions of the 1961 Convention and the corresponding national legislation. The Board urges all Governments that have not yet done so to examine their national policies, legislation, regulations and administrative procedures to identify and remove any obstacles to ensuring the adequate availability of opioids for treatment of moderate to severe pain. The Board requests the relevant international bodies, such as WHO and UNDCP, to further strengthen their support to developing countries in that field.

198. The Board notes with satisfaction that several Governments have taken steps to improve the availability of narcotic drugs. For example, in India, model regulations aimed at simplifying access to morphine for use in palliative care were developed by the Government, in cooperation with WHO, in 1998 and have since been introduced in several states in that country; workshops were organized to explain palliative care to drug control officials and to encourage their cooperation with health professionals in order to ensure improved access to morphine. In Italy, a new law on the use of analgesics came into force in March 2001; prescriptions for analgesics may now cover medication for a longer period of treatment and access to opioids to meet urgent requirements has been simplified.

199. The Board is concerned that, in many countries, particularly in Africa and Asia, the consumption of narcotic drugs for the treatment of moderate to severe pain continues to be extremely low. The Board reiterates its request to the Governments of the

countries concerned to look for ways to ensure appropriate access to analgesics.

Use of methylphenidate for the treatment of attention deficit disorder

200. The United States has always been the main consumer of methylphenidate, accounting in most years for around 85-90 per cent of global consumption of that substance.[56] In 2000, that country's share of global consumption of methylphenidate dropped to 70 per cent because of the large increase in consumption in other parts of the world. That development was also closely related to a recent sharp increase in the use of amphetamines (amphetamine and dexamfetamine) for the treatment of attention deficit disorder (ADD) in the United States. The use of amphetamines has already surpassed that of methylphenidate; amphetamines account for more than one half of the stimulants prescribed for the treatment of ADD. Total calculated consumption of stimulants for the treatment of ADD in the United States amounted to 9 defined daily doses per 1,000 inhabitants per day in 2000, a level comparable to almost three times the total consumption of all sedative-hypnotics in that country.

201. The Board trusts that the competent authorities of the United States will continue to carefully monitor developments in the diagnosis of ADD and other behavioural disorders and to ensure that amphetamines and methylphenidate are prescribed in accordance with sound medical practice as required under article 9, paragraph 2, of the 1971 Convention. The Board notes with concern that pharmaceutical companies have recently started publicly advertising methylphenidate preparations, including directly through consumer advertising campaigns in women's and other magazines and by distributing to the general public advertisements containing information on ADD. The Board notes that the authorities of the United States have asked the pharmaceutical companies to refrain from such advertising activities, particularly in the light of the fact that such activities are in contradiction with article 10, paragraph 2, of the 1971 Convention, on prohibiting the advertisement of psychotropic substances to the general public. The Board trusts that actions will follow to bring legislation in line with that Convention.

Stimulants used as anorectics

202. While consumption levels dropped significantly in the Americas, the consumption of anorectics has increased significantly in some countries and areas in South-East Asia, such as the Hong Kong Special Administrative Region of China, Malaysia and Singapore, and in Australia. European countries have reported divergent trends. While the consumption of anorectics has remained limited in most countries in Europe, others, such as Switzerland and the United Kingdom, have recorded remarkably increased rates. The Board requests Governments to carefully monitor the use of such substances in order to avoid their overprescription and possible abuse. The Board encourages Governments to ensure adequate control of domestic distribution channels for such substances, in order to prevent them from being diverted to illicit markets or smuggled into other countries, as the Board has repeatedly received reports of such occurrences during recent years.

203. In its report for 1998, the Board welcomed resolution S-20/4 A, adopted by the General Assembly at its twentieth special session, held in 1998, which contains the Action Plan against Illicit Manufacture, Trafficking and Abuse of Amphetamine-type Stimulants and Their Precursors.[57] The Board would like to remind Governments of their commitment to give high priority to measures against the abuse of amphetamine-type stimulants. Governments have confirmed their determination to detect and prevent the diversion of amphetamine-type stimulants from licit to illicit channels, as well as the irresponsible marketing and prescribing of such substances.

Consumption of buprenorphine

204. Buprenorphine, a potent opioid added to Schedule III of the 1971 Convention in 1989, has been in clinical use as an analgesic for many years. Buprenorphine has recently been introduced in the detoxification and substitution treatment of heroin addicts in several countries. In 2000, the Board initiated a survey of that use. In 2001, the Board followed up its survey with an investigation of the national control status of buprenorphine.

205. In the majority of countries reporting to the Board, buprenorphine is not controlled as a psychotropic substance but as a narcotic drug. During the last few years, its use in heroin substitution

treatment has been introduced in a number of countries (Australia, China, Denmark, France, Germany, India, Italy, Switzerland and the United Kingdom). Several other countries (the Netherlands, Poland, Turkey and the United States) have either reported the exceptional use of buprenorphine in substitution treatment or considered initiating its use in substitution treatment.

206. The worldwide manufacture of buprenorphine has been sharply increasing and is expected to increase further with the expanding use of that substance in substitution treatment. At the same time, the diversion of buprenorphine from domestic distribution channels and the smuggling and abuse of that substance have been reported in countries in Africa, Asia and Europe. As the availability of buprenorphine increases, its abuse may increase further as well. The Board, therefore, invites the Governments of all countries concerned to monitor carefully the use of that substance in order to prevent its diversion and abuse.

Consumption of other psychotropic substances

207. In recent years the particularly high benzodiazepine consumption levels in a number of European countries has led to the introduction of measures such as campaigns for raising the awareness of medical professionals and the general public, closer monitoring of prescription practices and tighter control mechanisms. The Board notes with appreciation that such measures have led to reductions in consumption levels in some of the most concerned countries, such as France. In this respect, the Board welcomes regional initiatives such as the meeting of the group of experts to examine the appropriate use of benzodiazepines, organized by the Pompidou Group of the Council of Europe in January 2001. The conclusions of the meeting resulted in further discussions by European countries, which ultimately led to the adoption by the Commission on Narcotic Drugs of resolution 44/13, entitled "Contribution to the appropriate use of benzodiazepines". In that resolution, the Commission addressed a number of matters referred to in the *Report of the International Narcotics Control Board* over the previous few years, including the appropriate prescription, dispensing and use of benzodiazepines, training for health professionals and information for patients.

G. Control of cannabis

208. Cannabis has been used in traditional medicine in some countries for centuries. In the early twentieth century, however, its recreational use became a social problem in traditional consumer countries, mainly in Asia. The 1925 International Opium Convention[58] included the first provisions on cannabis, which were aimed at preventing the export of cannabis resin to countries that prohibited its use and were intended to stop the illicit international trade in Indian hemp, especially the resin prepared from it.

209. There was no initiative to prohibit the traditional use of cannabis during the time of the League of Nations. It was only after the Second World War, in the 1950s, that a change in the attitude of the international community took place, as the traditional use of the drug began to be regarded as a form of abuse. Discussions began on the possibility of suppressing cannabis use, especially in Asia.

210. The new attitude was translated into the provisions of the 1961 Convention, which includes provisions on the control of cannabis. In that Convention, cannabis is defined as the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted. In the present chapter, cannabis is referred to in accordance with that definition. Cannabis has been included not only in Schedule I, but also in Schedule IV of the 1961 Convention, which requires the most stringent control measures. Parties to the 1961 Convention may adopt any additional control measures regarded as necessary, including prohibition, in the light of the particularly dangerous properties of the drugs listed in Schedule IV. To be included in Schedule IV, a drug has to be considered particularly liable to abuse and to produce ill effects, and such liability should not be offset by substantial therapeutic advantages. This was found applicable to cannabis in 1961. Countries where traditional use of cannabis existed were allowed a 25-year moratorium to phase out the use of cannabis for purposes other than medical and scientific purposes, in accordance with article 49 of the 1961 Convention.

211. Parties to the 1961 Convention are required to limit exclusively to medical and scientific purposes the production, manufacture, export, import and distribution of, trade in and use and possession of

RISK MANAGEMENT PLANS FOR RECENTLY APPROVED DRUGS*

Goal: To ensure safe use of the drug as labeled

COMPONENTS OF RISK MANAGEMENT PLANS	DRUG NAME
Restricted Prescribing: **Physician Agreement** **Physician Registry** **Restricted Specialty/Certification**	**Actiq, Fentanyl Oralet, Mifeprex, Thalomid**
Physician Education	**Accutane, Actiq, Thalomid**
Restricted Distribution: **Central Pharmacy** **Pharmacy Registration** **Hospital Pharmacy**	**Clozaril, Fentanyl Oralet, Mifeprex, Thalomid**
Limited Supply/Refills	**Actiq (C II), Thalomid**
Patient Agreement/Registry	**Accutane, Mifeprex, Thalomid**
Patient Education/Medication Guide	**Accutane, Actiq, Mifeprex, Thalomid**
Family Members & Caregivers Education/Emergency Numbers	**Actiq**
Safe Storage, Proper Handling and Disposal	**Actiq**
Restricted Advertisement	**Actiq, Fentanyl Oralet, Thalomid**
Special Reporting Agreement	**Actiq, Thalomid**

Approved Drugs: *

Accutane = isotretinoin

Actiq = Oral Transmucosal Fentanyl Citrate

Clozaril = clozapine

Fentanyl Oralet = Oral Transmucosal Fentanyl Citrate

Mifeprex = mifepristone

Thalomid = thalidomide

U.S. Food and Drug Administration

STATEMENT BY

John K. Jenkins

Director, Office of New Drug

Center for Drug Evaluation and Research

Food and Drug Administration

Department of Health and Human Services

For the Hearing on

Oxycontin: Balancing Risks and Benefits

Before the

U.S. Senate

Committee on Health, Education, Labor, and Pensions

February 12, 2002

Introduction

Mr. Chairman and Members of the Committee, I am John K. Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA or the Agency). I appreciate the opportunity to talk about the drug OxyContin and the steps that FDA has taken in an effort to decrease abuse and misuse of this product while assuring that this drug is used properly and remains available for patients who suffer daily from chronic moderate to severe pain.

Let me assure you that the Agency has taken reports of abuse and misuse of OxyContin very seriously and we have implemented aggressive steps in response to these reports. FDA has worked closely with the manufacturer of OxyContin, Purdue Pharma L.P., to strengthen the warnings and precautions sections of the approved labeling for OxyContin in order to educate physicians, other healthcare professionals, and patients regarding the serious, and potentially fatal, risks of abuse and misuse of

this product. FDA has also worked with Purdue Pharma to modify the approved labeling for OxyContin to emphasize that it is approved for the treatment of moderate to severe pain in patients who require around-the-clock narcotics for an extended period of time. FDA also has worked closely with the Drug Enforcement Administration (DEA) to address their concerns regarding abuse, misuse, and illegal diversion of OxyContin.

In order to help you to better understand FDA's actions, I would like to give you a brief overview of the process FDA followed in approving OxyContin and FDA's activities related to regulation of the promotion and marketing of OxyContin.

BACKGROUND

OxyContin is a narcotic drug that was approved by FDA for the treatment of moderate to severe pain on December 12, 1995. OxyContin contains oxycodone HCl, an opioid agonist with an addiction potential similar to that of morphine. Opioid agonists are substances that act by attaching to specific proteins called opioid receptors, which are found in the brain, spinal cord, and gastrointestinal tract. When these drugs attach to certain opioid receptors in the brain and spinal cord they can effectively block the transmission of pain messages to the brain. OxyContin is formulated to release oxycodone HCl in a slow and steady manner following oral ingestion. OxyContin is the only currently marketed FDA approved controlled-release formulation of oxycodone. The drug substance oxycodone, however, has been marketed in the U.S. for many decades and is available in a wide variety of immediate release and combination dosage forms.

Oxycodone, like morphine and other opioid agonists, has a high potential for abuse. OxyContin was specifically developed as a controlled release formulation by Purdue Pharma to allow for up to 12 hours of relief from moderate to severe pain. This dosage form allows patients with chronic moderate to severe pain to have their pain controlled for long periods of time without the need for another dose of medication and significantly reduces the number of tablets the patient must take each day.

When used properly, the OxyContin tablet must be taken whole and only by mouth. If the tablet is crushed, the controlled-release mechanism is defeated and the oxycodone contained in the tablet is all released at once. If the contents of an OxyContin tablet are injected intravenously or snorted into the nostrils a potentially lethal dose of oxycodone is released immediately. The risk of death due to abuse of OxyContin in this manner is particularly high in individuals who are not tolerant to opioids.

Oxycodone, the active ingredient in OxyContin, is a controlled substance in Schedule II of the Controlled Substances Act (CSA), 21 U.S.C. §801 et seq. which is administered by the DEA. Schedule II provides the maximum amount of control possible under the CSA for approved drug products. Schedule I drugs are considered to have no recognized medical purpose and are illegal in the U.S. outside of FDA approved research.

FDA DRUG APPROVAL PROCESS

Before any drug is approved for marketing in the U.S., FDA must decide--as quickly as a thorough evaluation allows--whether the studies submitted by the drug's sponsor

(usually the manufacturer) have adequately demonstrated that the drug is safe and effective under the conditions of use in the drug's labeling. It is important to realize; however, that no drug is absolutely safe. There is always some risk of adverse reactions with drugs. FDA's approval decisions, therefore, always involve an assessment of the benefits and the risks for a particular product. When the benefits of a drug are thought to outweigh the risks, and if the labeling instructions allow for safe and effective use, FDA considers a drug safe for approval and marketing.

OxyContin was reviewed by FDA and was approved for treatment of moderate to severe pain based on two clinical trials that demonstrated that it was safe and effective for this use. Prior to approval, FDA evaluated the benefits and risks of use of OxyContin for treatment of moderate to severe pain and determined that the drug was appropriate for use in this population when used according to the approved labeling.

During the approval process of OxyContin, as with all drugs that are active in the brain, FDA assessed its potential for abuse and misuse. Abuse liability assessments are based on a composite profile of the drug's chemistry, pharmacology, clinical manifestations, similarity to other drugs in a class, and the potential for public health risks following introduction of the drug to the general population. At the time of approval, the abuse potential for OxyContin was considered by FDA to be no greater than for other Schedule II opioid analgesics that were already marketed in the U.S. Based on the information available to FDA at the time of its approval, including the record of other modified release Schedule II opioids, the widespread abuse and misuse of OxyContin that has been reported over the past few years was not predicted. In fact, at the time of its approval, FDA believed that the controlled-release characteristics of the OxyContin formulation would result in less abuse potential since, when taken properly, the drug would be absorbed slowly and there would not be an immediate "rush" or high that would promote abuse. In part, FDA based its judgment of the abuse potential for OxyContin on the prior marketing history of MS-Contin, a controlled-release formulation of morphine that had been marketed in the U.S. by Purdue Pharma without significant reports of abuse and misuse for many years. At the time of OxyContin's approval, FDA was aware that crushing the controlled-release tablet followed by intravenous injection of the tablet's contents could result in a lethal overdose. A warning against such practice was included in the approved labeling. FDA did not anticipate, however, nor did anyone suggest, that crushing the controlled-release capsule followed by intravenous injection or snorting would become widespread and lead to a high level of abuse.

FDA ACTIONS

Labeling changes

In July 2001, Purdue Pharma, working in cooperation with FDA, significantly strengthened the warnings and precautions sections in the labeling for OxyContin. The labeling for OxyContin now includes a "black box" warning, the strongest warning for an FDA approved product, which warns patients and physicians of the potentially lethal consequences of crushing the controlled-release tablets and injecting or snorting the contents. The indication for use was clarified to reflect that it is approved for the treatment of moderate to severe pain in patients who require around the clock narcotics for an extended period of time.

To help in the effort to curb abuse and misuse of OxyContin, FDA has worked with Purdue Pharma to implement other specific changes in the OxyContin labeling. The new labeling is intended to highlight to physicians, other health care professionals, and patients that OxyContin should be used for the treatment of moderate to severe pain in patients who require around the clock narcotics for an extended period of time. As part of the labeling changes, a patient instruction sheet was added, which contains information to assist patients in the proper use of OxyContin. These labeling changes are an effort to educate pharmacists, other health professionals, and the general public regarding just how important it is to use this drug properly. The new warnings are intended to lessen the chance that OxyContin will be prescribed inappropriately for pain of lesser severity than the approved use or for other disorders or conditions inappropriate for a Schedule II narcotic.

FDA has developed a patient-information page on its website (www.fda.gov/cder/drug/infopage/oxycontin/default.htm). This site provides important information to patients regarding how to safely use OxyContin, urges patients to keep their supply of OxyContin in a secure location, and instructs patients to destroy unneeded tablets.

As part of a longer-term strategy to address the current reports of abuse and misuse of OxyContin, Purdue Pharma has informed FDA that the company is working to reformulate OxyContin. The reformulation would add an opioid antagonist that would counteract the effects of oxycodone, the active ingredient in OxyContin, if the OxyContin tablet were crushed into a powder and injected or snorted. FDA is working actively with Purdue Pharma to evaluate the safety and effectiveness of such a reformulated product. It must be noted that such a reformulation is not a simple task and it could be several years before any new combination product is developed, tested in clinical trials, and approved by FDA. It also must be noted that the addition of the opioid antagonist to OxyContin to deter abuse means that legitimate patients would be exposed to a drug substance that they do not need. This could result in adverse reactions in such legitimate patients. These potential safety issues, and assurance that the combination tablet retains its effectiveness in treating moderate to severe pain, must be a part of FDA's review of a reformulated OxyContin product.

Letters to health care professionals

There have been numerous reports of OxyContin diversion and abuse in several states. Some of these reported cases have been associated with serious consequences including death. In an effort to educate health care providers about these risks, Purdue Pharma has issued a warning in the form of a "Dear Healthcare Professional" letter. The "Dear Healthcare Professional" letter was distributed widely to physicians, pharmacists, and other health professionals. The letter explains the changes to the labeling, including proper prescribing information and highlights the problems associated with the abuse and diversion of OxyContin.

FDA approved indication for OxyContin is for the treatment of patients with moderate to severe pain who require around-the-clock opioids for an extended time. An important factor that must be considered in prescribing OxyContin is the severity of the pain that is being treated, not simply the disease causing the painful symptoms.

FDA continues to recommend that appropriate pain control be provided to patients who are living with moderate to severe pain. Although abuse, misuse, and diversion are potential problems for all opioids, including OxyContin, they are a very important part of the medical armamentarium for the management of pain when used appropriately under the careful supervision of a physician.

Meeting with other government agencies and industry

FDA has met with DEA, the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, the Office of National Drug Control Policy, the Centers for Disease Control and Prevention and Purdue Pharma, and continue to work collaboratively sharing information and insights needed to address the problem of OxyContin abuse and diversion.

Millions of Americans suffer from some form of chronic pain. The pain can be debilitating and often prevents those afflicted from working or even leaving their home. Many medications, including opioids, play an important role in the treatment of chronic pain. Opioids, however, often have their use limited by concerns regarding misuse, addiction, and possible diversion for non-medical uses. The use of opioid therapy in some patients has shown extraordinary promise, enabling some to return to work and to lead a normal life again. FDA is committed to continuing to work with other government agencies and sponsors to insure that options are available to patients with chronic moderate to severe pain, so that in consultation with their personal physician they can achieve as normal a life as possible.

Advisory Committee Meetings

An FDA advisory committee, a group of non-Agency experts, held a meeting on January 30-31, 2002, to discuss the medical use of opioid analgesics, appropriate drug development plans to support approval of opioid analgesics, and strategies to communicate and manage the risks associated with opioid analgesics, particularly the risks of abuse of these drugs. Committee members agreed that opioids are essential for relieving pain and that a great deal of progress has been made within the last few years to remove the stigma associated with opioid treatment. Members suggested that a balanced approach should be taken to relieve pain for patients and to prevent diversion. They noted that imposing restrictions on use of opioids could have substantial likelihood of hurting legitimate patients and reversing the tremendous progress that has been achieved in the appropriate treatment of pain.

FDA will continue to monitor reports of abuse, misuse, and diversion of OxyContin and other opioids and will work with other Federal agencies and drug manufacturers to help ensure that these important drugs remain available to appropriate patients.

DRUG ADVERTISING

FDA has regulated the advertising of prescription drugs since 1962, under the Food, Drug, and Cosmetic (FD&C) Act and its implementing regulations. The Division of Drug Marketing, Advertising, and Communications (DDMAC), in CDER, is responsible for regulating prescription drug advertising and promotion. DDMAC's mission is to protect

the public health by insuring that prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement, and education program, and by fostering optimal communication of labeling and promotional information to both health care professionals and consumers.

FDA regulates prescription drug advertisements and other promotional materials (called "promotional labeling") disseminated by or on behalf of the advertised product's manufacturer, packer or distributor to health care professionals and consumers.

Title 21 of the Code of Federal Regulations (21 CFR §314.81(b)(3)(i)) requires that advertisements and promotional labeling be submitted to FDA at the time of initial dissemination (labeling) and initial publication (advertisements); a post-marketing submission requirement. The FD&C Act generally prohibits FDA from requiring that advertisements be approved prior to their use (see §502(n)). In other words, FDA's review of promotional materials is generally intended to occur post hoc - once the materials have already appeared in public. Accordingly, any FDA enforcement action that FDA takes is *post hoc* as well. Most of FDA's enforcement actions request that sponsors stop using the violative materials. In some cases, FDA also asks sponsors to run corrective advertisements or issue corrective letters to remedy inaccurate product impressions created by false or misleading materials.

FDA is not aware of any direct-to-consumer advertising for OxyContin. There is nothing in the FD&C Act to prohibit such advertising. The advertising and marketing for OxyContin has been directed only to health care professionals. It should be noted that the current approved product labeling for OxyContin contains a "black box" warning. Boxed warnings are used in labeling to convey serious risks associated with the use of the drug product. The promotional materials of drug products with boxed warnings must present these serious risks in a prominent manner. DDMAC sent a letter to Purdue Pharma dated May 11, 2000, regarding a journal advertisement that appeared in the *New England Journal of Medicine* that promoted OxyContin in a manner that was false or misleading. Specifically, the advertisement implied OxyContin had been studied in all types of arthritis and can be used as first-line therapy for the treatment of osteoarthritis, failed to include important limitations to claims presented from an osteoarthritis study; and promoted OxyContin in a selected class of patients without presenting risk information especially applicable to that selected class of patients. Purdue Pharma agreed to cease dissemination of this advertisement and this matter was resolved with the cooperation of the sponsor.

CONCLUSION

The Agency recognizes OxyContin as a valuable product when used properly. We need to do all we can to ensure that the prescriptions get to the appropriate patients and that labeling and promotion are appropriate for the product. FDA is working closely with the manufacturer to take appropriate action to curb the misuse and abuse of OxyContin. In addition, FDA is involved in the strong interagency effort to address this issue and we are aware we cannot solve this problem by ourselves.

We share the Committee's interest and concerns regarding this drug and would be happy to answer any questions.

Recent Testimonies
